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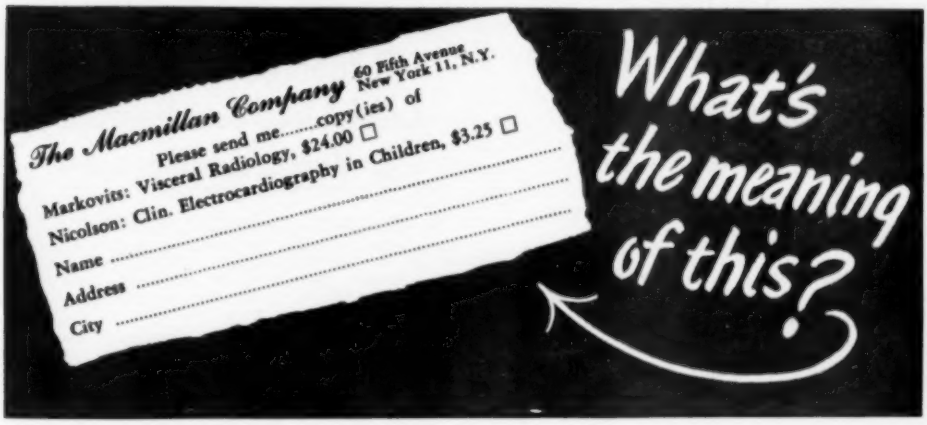
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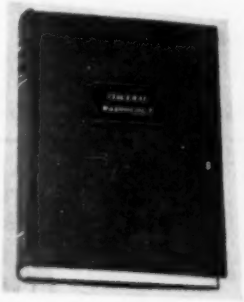

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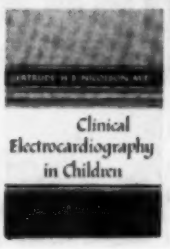

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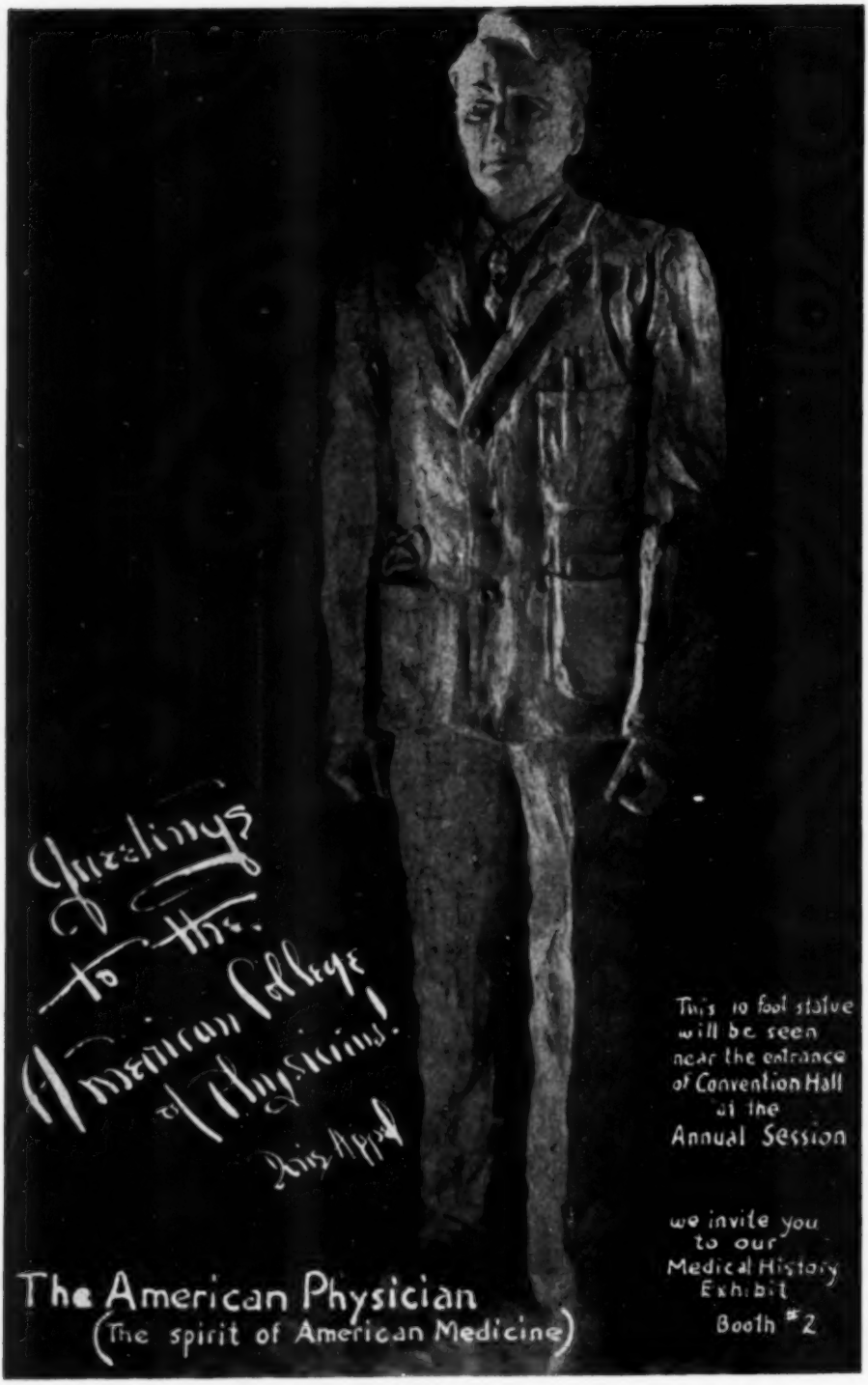
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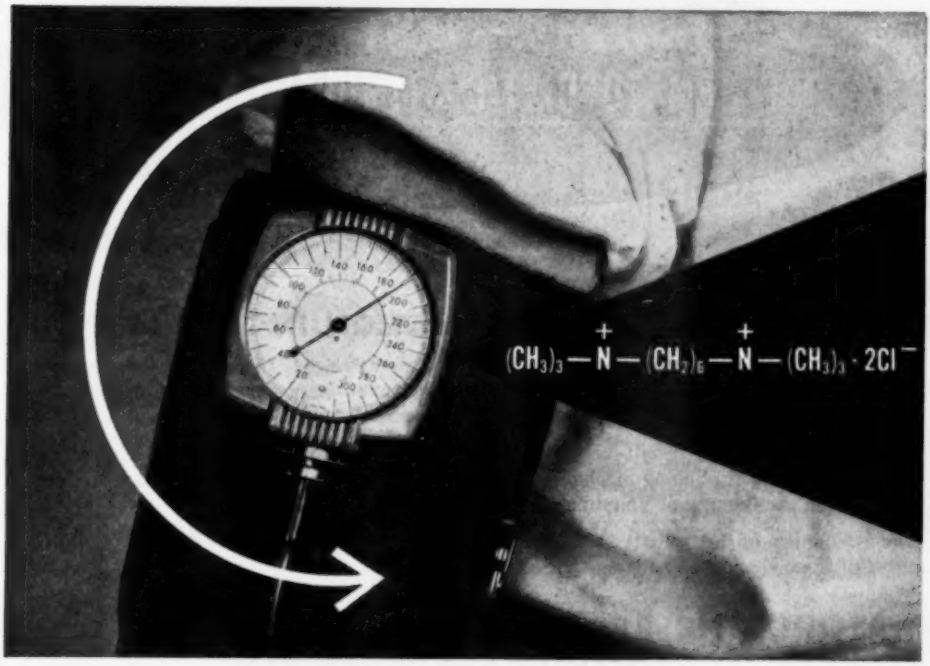

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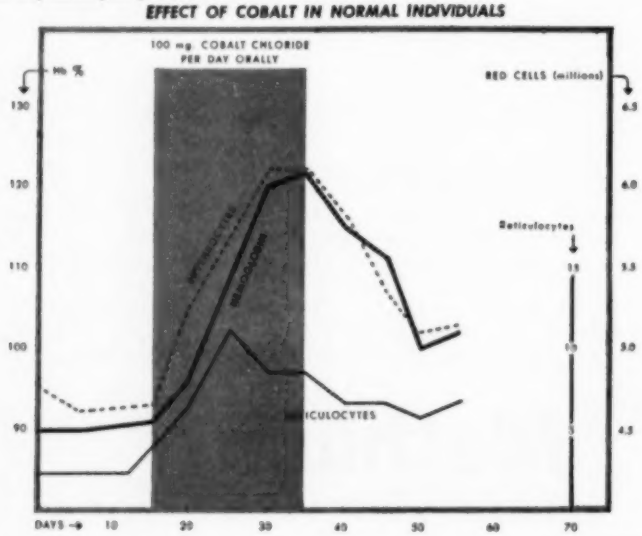

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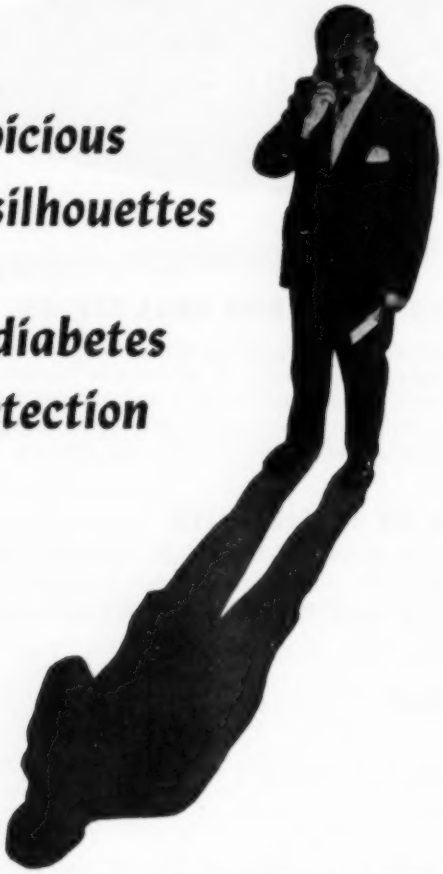

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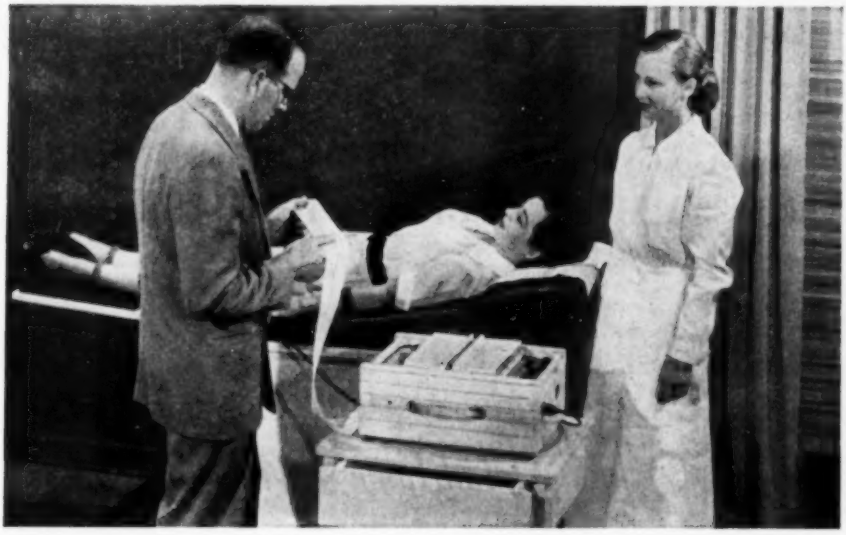

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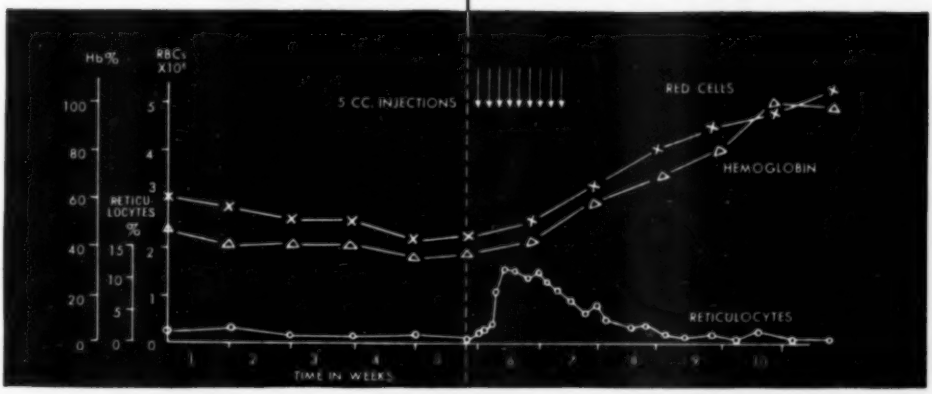

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1. Dickstein, B., et al.: Am. J. Dis. Child. 84:52 (July) 1952.

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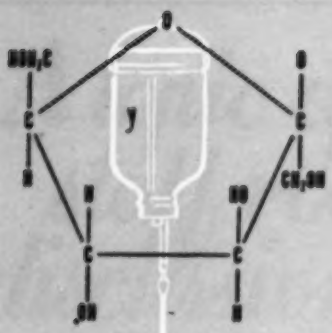


presenting

Levugen

(FRUCTOSE, MEAD)

fructose (levulose) for intravenous infusion . . . now, for the first time, available for general clinical use

The advantages of fructose for intravenous infusion have long been recognized.[1,2] But limited availability of pure fructose has prevented its general clinical use.

Now, extensive research in carbohydrate chemistry by Mead Johnson & Company has resulted in a practical and economical method of producing pure fructose. As Levugen 10% in Water, it is available for intravenous use.

"Levugen *can be infused more rapidly*"

Levugen (Fructose, Mead) can be infused much more rapidly than dextrose, with better retention and less disturbance of fluid balance

Since Levugen is removed from the blood very rapidly, it does not produce high hyperglycemic levels or spill over into the urine in significant amounts even when it is infused in fairly high concentration.[1,2,3] Levugen can therefore be given much more rapidly than dextrose, with less loss of potential calories through glycosuria. A liter of Levugen 10% in Water can be given in the same time as a liter of 5% dextrose.

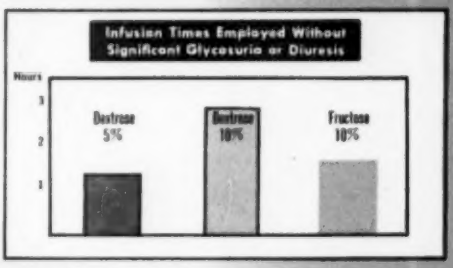
Experimental evidence indicates, moreover, that Levugen is more rapidly and completely utilized for hepatic glycogen formation than is dextrose.[1,4]

Clinical Advantages of Levugen

- More rapid and adequate provision of calories
- Less loss of calories through glycosuria
- More rapid formation of liver glycogen
- Less disturbance of fluid balance
- Shorter infusion time, with less discomfort for the patient
- Less time and trouble for hospital personnel

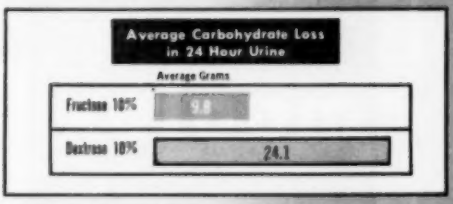
Levugen 10% in Water is available in 1 liter (1000 cc.) flasks, containing 100 Gm. of Levugen (Fructose, Mead), approximately 400 calories.

LEVUGEN GIVEN TWICE AS RAPIDLY AS DEXTROSE



Based on infusion rates per liter reported by Lockhart and Elman[2] (for dextrose) and Weichselbaum et al.[3] (for fructose).

MUCH LESS URINARY LOSS OF CALORIES WITH LEVUGEN



Based on data from Elman.[5] Infusion of 2 liters of each solution into the same subjects on alternate days.

References: (1) Nutrition Rev. 9: 173-175, 1951; (2) Weichselbaum, T. E., et al.: Proc. Soc. Exper. Biol. & Med. 75: 816-818, 1950; (3) Lockhart, C. E., and Elman, R.: Surg., Gynec. & Obst. 88: 97-102, 1949; (4) Cori, C. F.: J. Biol. Chem. 70: 577-588, 1926; (5) Elman, R.: Personal Communication.

Levugen

(FRUCTOSE, MEAD)

MEAD JOHNSON & COMPANY • EVANSVILLE 21, IND., U.S.A.

MEAD

maalox

for gastric hyperacidity in peptic ulcer

Suspension MAALOX—Rorer provides the *hydroxides* of Magnesium and Aluminum in colloidal form . . . pleasantly flavored and highly acceptable, even with prolonged use. Relief of pain and epigastric distress is prompt and long-lasting. Freedom from constipation and side effects common to other antacids is noteworthy.

supplied:
in 355 cc. (12 fluidounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension.)

Samples will be sent promptly upon request.

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In early Rheumatoid arthritis

to increase and accelerate the appearance of remissions

"Gold salts, if administered during the first year of rheumatoid arthritis, increase and accelerate the appearance of remissions."* A remission rate of 66 per cent was recently noted in a group of gold-treated patients with rheumatoid arthritis of 12 months or less duration. Similar patients treated without gold showed a remission rate of only 24.1 per cent. On the average, remissions appeared 10 months sooner in the gold-treated cases.

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*Adams, C. H., and Cecil, R. L.: Ann. Int. Med. 33:165, 1950.

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a potent, new direct acting antibiotic

FUMIDIL is direct acting

FUMIDIL, unlike the broad spectrum antibiotics, is directly amebicidal. It has no antibacterial spectrum, and does not affect normal flora in the intestinal tract.

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FUMIDIL acts specifically against *E. histolytica* without effect upon the bacteria present. Thus, the danger of overgrowth of yeasts and fungi is slight. Reported studies show low incidence of recurrence.

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1-132

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16 **ONE-HALF GRAM** ENTERIC-COATED
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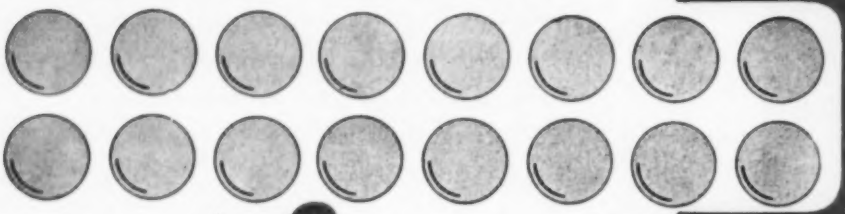

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of ammonium chloride
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well tolerated
broad spectrum antibiotic

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in the pneumonias

Highly effective in a wide range of bacterial, rickettsial, and viral pneumonias, CHLOROMYCETIN (chloramphenicol, Parke-Davis) is particularly valuable in mixed infections and where the causative agent is not easily ascertained.

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Parke, Davis & Company

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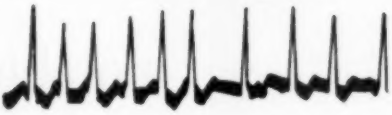
and down



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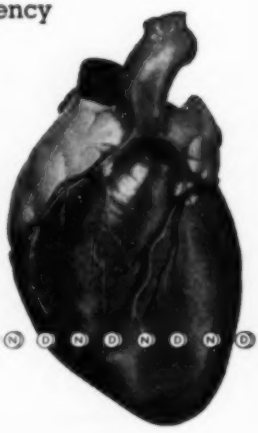

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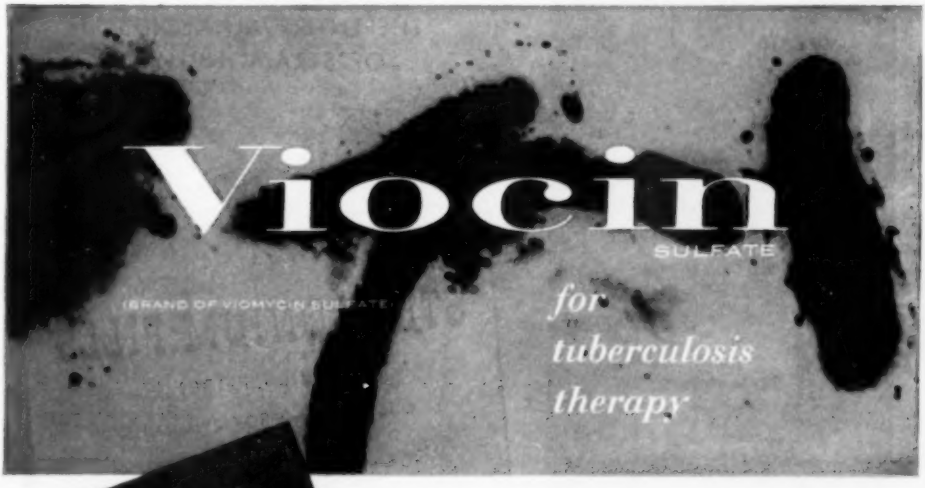

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0.15 GRAM (APPROX. 2½ GRAINS)

These pills exhibit the powdered dried leaf and flowering top of Datura Stramonium, alkaloidally assayed and standardized, and therefore contain in each pill 0.375 mg. (1/170 grain) of the alkaloids of stramonium.

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Cardalin tablets

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offer distinct advantages over any other dosage form of aminophylline

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Cardalin—Each Cardalin tablet contains: Aminophylline, 5 grains; Aluminum Hydroxide, 2.5 grains; Ethyl Aminobenzoate, 0.5 grains. Cardalin is best tolerated after meals and preferably administered with one-half glassful of milk.

Cardalin-Phen now available containing phenobarbital (¼ gr. per tablet).

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Delicious-tasting Dietene Milk Shake (skimmed milk and Dietene) provides maximal amounts of protein, vitamins and minerals with a minimum of calories. Taken in mid-morning and mid-afternoon, it satisfies the appetite for food and makes it easier for the patient to adhere to his diet.

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*COPPER	0.7 mg.	FOLIC ACID	0.05 mg.
FLUORINE	3.0 mg.	*NIACIN	6.7 mg.
*IODINE	0.15 mg.	PANTOTHENIC ACID	3.0 mg.
*IRON	12 mg.	PYRIDOXINE	0.6 mg.
MAGNESIUM	120 mg.	*RIBOFLAVIN	2.0 mg.
MANGANESE	0.4 mg.	*THIAMINE	1.2 mg.
*PHOSPHORUS	940 mg.	*VITAMIN A	3200 I.U.
POTASSIUM	1300 mg.	VITAMIN B_{12}	0.005 mg.
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ZINC	2.6 mg.		

*PROTEIN (biologically complete)	32 Gm.
*CARBOHYDRATE	65 Gm.
*LIPIDS	30 Gm.

*Nutrients for which daily dietary allowances are recommended by the National Research Council.

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Tryptar is also effective in the everyday management of varicose ulcers, in burns, soft tissue abscesses, osteomyelitis, fistulae and sinus tracts.

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BENTYL ..... 10 mg.
when sedation is desired
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1. Hufford, A. R., Rev. of Gastroenterology, 18:588, 1951
2. Miller, B. N., J. So. Carolina M. A., 48:1, 1952

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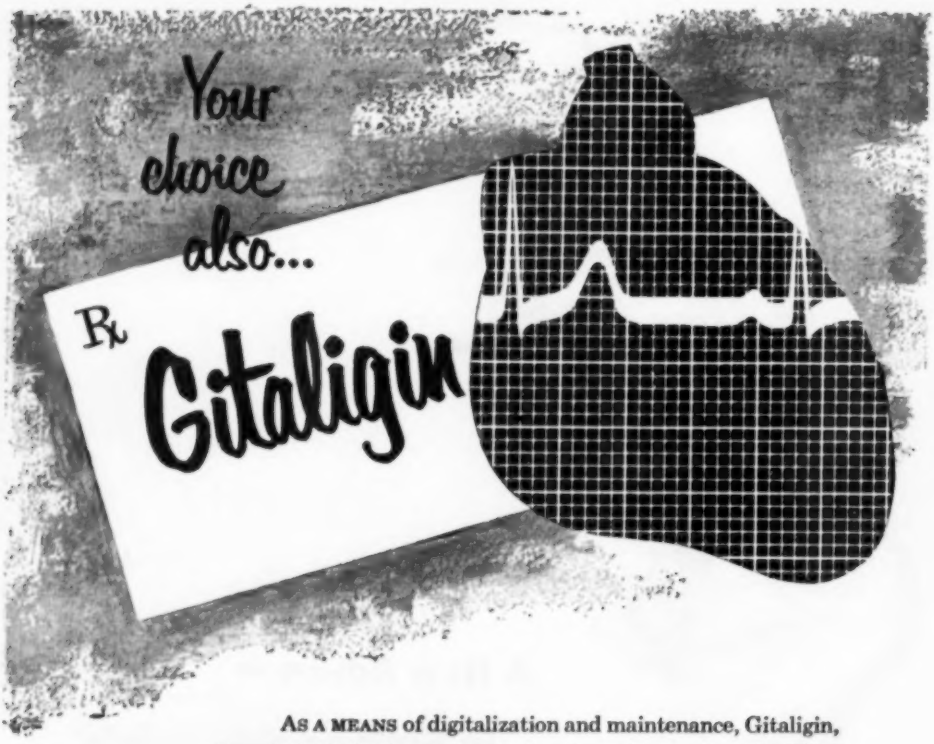

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1. Batterman, R. C.; DeGraff, A. C.; Gutner, L. B.; Rose, O. A., and Lhowe, J.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, Am. Heart J. 42:292-307 (Aug.) 1951.

2. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: The Therapeutic Range of Gitalin (amorphous) Compared with other Digitalis Preparations, Circulation 5:201-207 (Feb.) 1952.

3. Nalefski, L.: Personal Communication

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"The latent period between the initiation of therapy and the appearance of appreciable benefit was short."[1]

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BUTAZOLIDIN brings quick relief and, often, functional improvement, to the majority of patients with rheumatoid arthritis, osteoarthritis, spondylitis, gout, arthritis with psoriasis, peritendinitis, fibrositis, and other painful musculoskeletal disorders.[1-3]

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1. Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: Paper read before the Annual Meeting of the American Rheumatism Association, Chicago, Ill., June 6, 1952.
2. Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952.
3. Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952.

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- **or cloying taste**—delicious alone or with a variety of nutritious foods

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Vol. 36, No. 1, January, 1952

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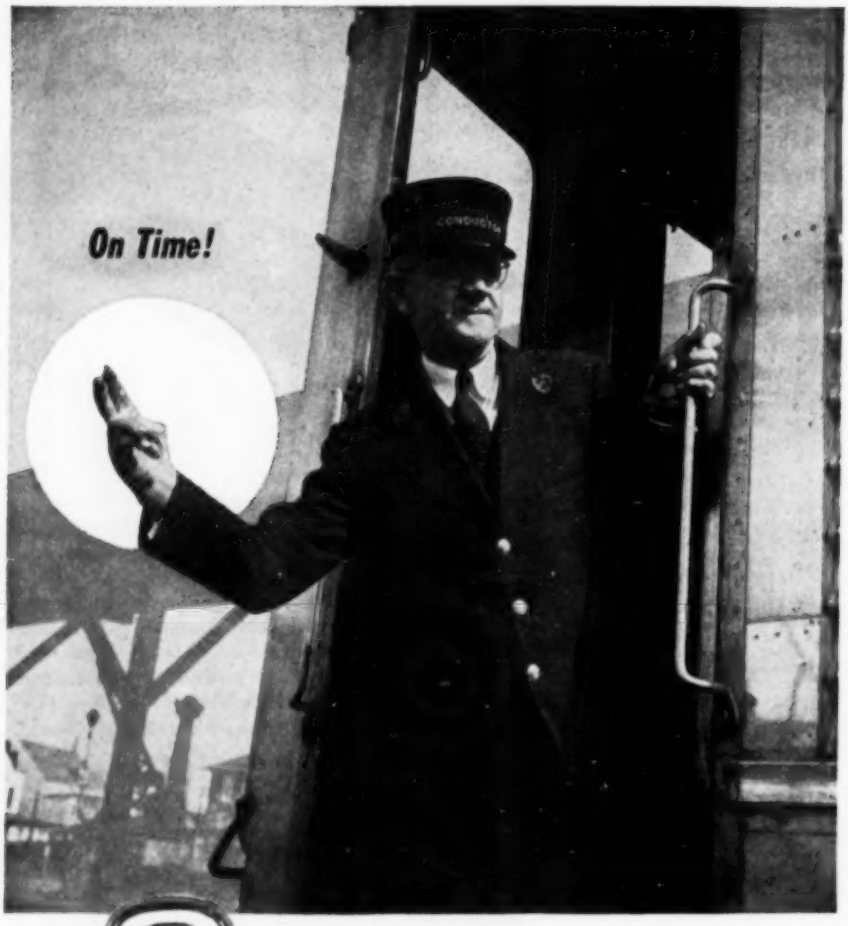

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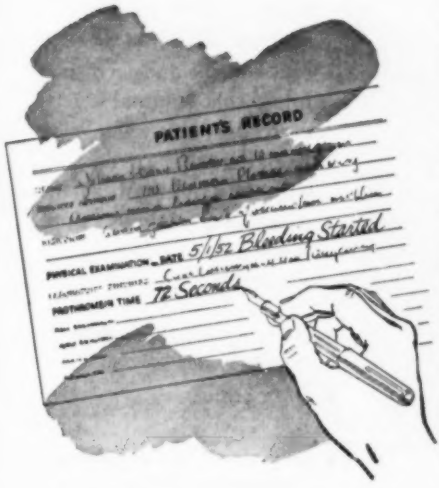

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McCLINTOCK, J. C., AND LYONS, J. A.: N. Y. STATE J. MED. 51:1628, 1951

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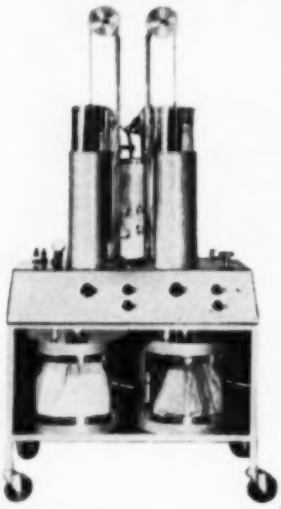

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He concludes that L.A. Formula "provides a natural, unabsorbable bulk and lubricant with no clinical disadvantages. It offers many advantages over mineral oil and has none of mineral oil's disadvantages." *Burton, Parsons & Company, Washington 9, D. C.*

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1. Cantor, A. J., Am. J. Proctol. 3:204-210, (Sept.) 1952.

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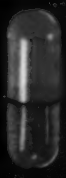

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Keefer[4] has stated that in most cases, "therapeutic results that follow oral therapy are comparable in every way to those following parenteral therapy."

1. Brit. M.J. *2*:1361, 1951
2. Brit. M.J. *2*:1365, 1951
3. Am. J. Med. *3*:216, 1949
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ANNALS OF
INTERNAL MEDICINE

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IMMUNOLOGIC MECHANISMS IN IDIOPATHIC AND NEONATAL THROMBOCYTOPENIC PURPURA *

By WILLIAM J. HARRINGTON, M.D.,† *St. Louis, Missouri,* CHARLES C. SPRAGUE, M.D., *New Orleans, Louisiana,* VIRGINIA MINNICH, M.S., CARL V. MOORE, M.D., F.A.C.P., ROBERT C. AULVIN, B.S., and REUBENIA DUBACH, Ph.D., *St. Louis, Missouri*

THE mechanisms responsible for the low platelet count in idiopathic thrombocytopenic purpura are not well understood despite the careful studies by many competent investigators. The thrombocytopenia has been attributed to:

1. A decrease in the rate of platelet formation from megakaryocytes [1, 2] because of splenic inhibition of these cells; [3, 4, 5, 6]
2. An increase in the rate of platelet destruction by the spleen, [7, 8, 9, 10, 11, 12] and
3. A combination of damage to both megakaryocytes and circulating platelets. [13, 14]

Evidence to support the latter concept has been presented recently. A thrombocytopenic factor which damages circulating platelets and probably also suppresses the formation of platelets from megakaryocytes was demonstrated in the plasma of eight out of 10 patients with idiopathic purpura. [15, 16] In the present paper, observations are reported to indicate that the thrombocytopenic factor may be a platelet agglutinin, and that those patients with idiopathic thrombocytopenic purpura who do not have platelet antibodies develop their disease solely because of a deficiency in platelet production.

* Presented (in part) at the Thirty-third Annual Session of the American College of Physicians, Cleveland, Ohio, April 23, 1952.

From the Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri.

This work was supported by Grant No. H-22 C (6) from the National Heart Council of the U. S. Public Health Service, Bethesda, Maryland.

† On assignment from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

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The suggestion is made that idiopathic thrombocytopenic purpura is a syndrome which therefore may be caused by several different mechanisms. In addition, the rôle of the spleen in idiopathic thrombocytopenia is analyzed, the pathogenesis of neonatal thrombocytopenia is discussed, and evidence suggesting the existence of serologically distinguishable platelet types is described.

I. Case Material and Technics Employed

Thirty-five patients with idiopathic thrombocytopenic purpura have been studied. The diagnosis in each instance was made only after thorough examination of the peripheral blood and bone marrow, and exclusion of other etiologic factors. In 22 instances the syndrome was acute; in 13, it was chronic. There were 26 women, five men and four children. Pertinent data on each case are summarized in table 1.

In vivo and in vitro methods of investigation were employed. The former consisted of noting the effects produced by transfusing 500 c.c. of whole blood or its plasma equivalent obtained from 26 of these patients into volunteer recipients who were either normal subjects from the laboratory or patients with inoperable malignant neoplasms. Platelet counts, red cell counts, and white cell counts were followed closely in all instances. In some cases repeated observations were made of the coagulation time in siliconed tubes, clot retraction, prothrombin consumption, bleeding time, capillary fragility and bone marrow morphology. Reference has previously been made to the technics utilized.[15] The indirect method was used for counting platelets except in the animal experiments, as noted below. A decrease of approximately 50 per cent in the recipient's platelet count which persisted for from four to seven days was regarded as evidence for the presence of a circulating thrombocytopenic factor in the donor's plasma. Thrombocytopenia of greater magnitude was frequently induced.

The plasma of 31 patients was examined by an in vitro test for platelet agglutinins. The following reagents and materials were employed:

1. Silicone ("Drifilm SC-87," General Electric Chemical Division, Pittsfield, Massachusetts), diluted 1:10 with petroleum ether.
2. "Arquad 2C" (Armour Chemical Division, Chicago 9, Illinois).
3. "Parafilm" (Marathon Corporation, Menasha, Wisconsin).
4. No. 18 gauge needles.
5. Glass tubes 16 × 125 mm., 10 × 75 mm.
6. Micro test slides, depressed cell type.
7. Ethylene diamine tetraacetic acid, disodium salt ("Sequestrene, Na2," Alrose Chemical Company, Providence, Rhode Island). Five per cent solution in distilled water.
8. Citric acid, 1/3 N.
9. Whatman No. 50 filter paper.
10. Small glass funnels.
11. Large bore 1 c.c. pipettes graduated in tenths of a c.c.

TABLE I

Idiopathic Thrombocytopenic Purpura

Case No.	Patient	Age	Sex	Duration of Disease	Severity of Disease*	Therapy	Outcome	History of		Comments	Tests†		
								Transfusions	Pregnancy		In Vivo	In Vitro	
												All Platelets	Some Platelets
Acute													
1	C. D.	39	M.	1 mo. 3rd episode in 10 years.	+	None	Spontaneous remission	−	−	Tests positive only during thrombocytopenia	+	+	+
2	R. S.	31	F.	10 mos severe for 1 mo.	++	Cortisone Splenectomy	Suboptimal platelet rise. Remission	−	−		+	+	+
3	F. B.	51	F.	3 mos	++	Cortisone	Incomplete platelet rise. Spontaneous remission	−	−	Tests positive only during thrombocytopenia	+	+	+
4	C. S.	48	F.	1½ mos. 3rd episode in 10 yrs.	++	Splenectomy	Remission	−	−	Autoagglutination demonstrated	+	−	+
5	B. P.	63	F.	5 mos.	++	Splenectomy	Remission	−	+	Transient relapse in four months	+	+	+
6	G. M.	35	F.	1 week. Relapse 5 yrs. post-splenectomy	++	Cortisone	Remission	+	+	Tests positive only during thrombocytopenia	+	0	0
7	E. T.	63	F.	6 weeks	+++	Splenectomy	Remission	−	+		+	+	+
8	L. P.	19	F	2 weeks	+++	Cortisone Splenectomy	No response. Remission	+	+	Pregnant—baby thrombocytopenic	+	+	+

TABLE I—*Continued*

Case No.	Patient	Age	Sex	Duration of Disease	Severity of Disease*	Therapy	Outcome	History of		Comments	Tests†		
								Transfusions	Pregnancy		In Vivo	In Vitro	
												All Platelets	Some Platelets
9	C. K.	6	F.	4 weeks	+++	Cortisone Splenectomy	No platelet rise. Remission	+	−	Also acquired hemolytic anemia with positive antiglobulin test	0	+	+
10	L. N.	68	F.	1 mo.	++++	Splenectomy Cortisone	No platelet rise. Remission	+	+	Also acquired hemolytic anemia with positive antiglobulin test. Autoagglutinins demonstrated	0	−	+
11	M. J.	32	F.	6 weeks	+++	Splenectomy	Remission	+	+		0	−	+
12	L. S.	59	F.	5 weeks	+++	Splenectomy	Remission	+	+	In vitro test only weakly positive after remission	0	−	+
13	F. C.	46	F.	3 mos.	++++	Splenectomy ACTH Cortisone	No change No change No change	+	−	Spontaneous though incomplete remission after 2 yrs.	+	+	+
14	M. L.	41	F.	3 mos.	++++	Splenectomy Cortisone	No change. Death, subarachnoid hemorrhage	+	+	No accessory spleen at post mortem	+	+	+
15	S. P.	17	M.	2 mos.	++++	Splenectomy	No change. Death, intracerebral hemorrhage	+	−	No accessory spleen at post mortem	+	−	+
16	M. W.	42	F.	2 weeks	+	Cortisone	Remission	−	−		−	0	0
17	W. S.	27	F.	1 mo.	+ +	ACTH	Remission	−	+		−	−	−

TABLE I—*Continued*

Case No.	Patient	Age	Sex	Duration of Disease	Severity of Disease*	Therapy	Outcome	History of		Comments	Tests†		
								Transfusions	Pregnancy		In Vivo	In Vitro	
												All Platelets	Some Platelets
18	L. J.	36	F.	1 week	+++	Splenectomy	Incomplete remission following Cesarean section and splenectomy	−	+	Infant normal	0	−	−
19	S. H.	19	F.	1 mo.	+++	ACTH Splenectomy	No effect. Remission concomitant with delivery	+	+	Infant normal	−	−	−
20	N. S.	71	F.	1 mo.	++	Splenectomy	Gradual but suboptimal platelet increase	−	+		0	−	−
21	I. B.	28	F.	1 mo.	++	ACTH Transfusion of platelet-rich blood	No response. Remission	−	+	Also moderate granulocytopenia. Normal survival of transfused platelets	−	−	−
22	V. A.	32	F.	1 week	+	Splenectomy	No response	−	−		−	0	0
							Chronic						
23	R. C.	7	M.	1 year	++	Cortisone Splenectomy	No platelet increase. Remission	−	−		+	−	+
24	B. T.	23	F.	8 years	++	Splenectomy	Remission	+	+	Gave birth to 2 thrombocytopenic infants	0	+	+

TABLE I—*Continued*

Case No.	Patient	Age	Sex	Duration of Disease	Severity of Disease*	Therapy	Outcome	History of		Comments	Tests†		
								Transfusions	Pregnancy		In Vivo	In Vitro	
												All Platelets	Some Platelets
25	M. H.	34	F.	12 years	++++	Splenectomy	Suboptimal platelet increase	+	+	Gave birth to 5 thrombocytopenic infants. Auto-agglutinins demonstrated	+	−	+
26	H. S.	30	M.	10 years	+	ACTH Cortisone Splenectomy	No response No response No response	+	−		+	+	+
27	A. J.	29	F.	2 years	++++	ACTH Cortisone Splenectomy	No response. Death, subarachnoid and intracerebral hemorrhage	+	+	No accessory spleen at post mortem	+	−	+
28	D. G.	52	F.	7 years	+	None to date	Status quo	−	+	Autoagglutinins demonstrated	±	−	+
29	S. F.	8	F.	1 year	++	Cortisone Splenectomy	No response. Remission	−	−		0	−	−
30	V. G.	56	M.	9 years	+	Splenectomy	Gradual, suboptimal platelet increase	−	−		−	−	−
31	R. L.	27	F.	10 years	++	Splenectomy	No response	+	+	Intermittent granulocytopenia. No agglutinins against own platelets	−	−	+
32	J. B.	62	M.	1 year	++++	ACTH Cortisone Splenectomy	No response No response No response	+	−		−	−	−

TABLE I—*Continued*

Case No.	Patient	Age	Sex	Duration of Disease	Severity of Disease*	Therapy	Outcome	History of		Comments	Tests†		
								Transfusions	Pregnancy		In Vivo	In Vitro	
												All Platelets	Some Platelets
33	M. S.	60	F.	10 years	+	ACTH Cortisone Splenectomy	No response No response No response	+	−	No agglutinins against own platelets	−	−	+
34	D. T.	38	F.	1 year	++++	ACTH Cortisone Splenectomy	No response No response No response	+	+		−	−	−
35	N. J.	2	M.	18 mos.	+++	Splenectomy	Gradual, suboptimal platelet increase	−	−		−	−	−

* Severity of disease: + = Easy bruising, few petechiae, no incapacitation or blood loss. ++ = Moderately severe purpura, moderate blood loss but no incapacitation. +++ = Severe purpura requiring transfusions to avoid incapacitation. ++++ = Severe purpura, severe blood loss, marked incapacitation.

† 0 = Tests not done. + = Positive results. − = Negative results.

Method: The citric acid, Sequestrene solution and platelet-free plasmas or sera are filtered prior to use. All glassware and needles which come into contact with platelets are siliconed. Needles may alternatively be coated with Arquad.

Ten cubic centimeters of venous blood are allowed to flow directly into a tube containing 0.3 c.c. of the Sequestrene solution. No syringe is employed, and only moderate tourniquet pressure is used. Prior to collection in the tube a few cubic centimeters of blood are allowed to flow into a gauze flat under the hub of the needle.

The tube is capped with Parafilm and inverted once to assure adequate mixing. It is then centrifuged at 200 G. for 30 minutes (1,000 RPM in an International Centrifuge Size 1, Type SB). One or 2 c.c. of supernatant platelet-rich plasma are decanted into another tube and placed in a refrigerator at 5° C. until used. This is the platelet suspension. A few hours may elapse before it is used. The remainder of the blood is centrifuged at 2,700 G (3,700 RPM) for 30 minutes. The supernatant plasma is platelet-free and is used as the source of antibody. Sterile serum may also be used 24 hours after blood has clotted at 37° C. in nonsiliconed tubes; 0.06 c.c. of the Sequestrene solution is added to each cubic centimeter of serum. The platelet-free plasma or serum is acidified with 1/3 N citric acid in a proportion of 0.1 c.c. of the acid for each 0.9 c.c. of serum or plasma.* Acidified serum or plasma should be used on the same day it is prepared.

One tenth cubic centimeter aliquots of platelet-rich (nonacidified) and platelet-free (acidified) plasma are placed in 10 mm. tubes, agitated, and either capped with Parafilm or covered with a moist towel. The tubes are then placed in a 37° C. waterbath for one hour and in a 5° C. refrigerator for two additional hours (or may be left for one more hour at 37° C.). Control studies are carried out with each platelet suspension in its own acidified serum or plasma. The tubes are then centrifuged at 200 G. for two minutes, tapped gently 10 times, and poured onto depressed-cell slides. Platelet agglutination is read microscopically under low magnification and graded 1 plus to 4 plus (figure 1). Sequestrene is anticomplementary in concentrations at least as small as four parts per thousand,† a dilution greater than that employed in this test. Therefore, lysis of agglutinated platelets would not occur if complement were necessary.

For titering purposes, 22 per cent bovine albumin to which 0.04 c.c. of the Sequestrene solution and 0.06 c.c. 1/3 N citric acid per cubic centimeter have been added is employed as the diluent. Globin, polyvinylpyrrolidone,

* The acidification procedure is a modification of the technic of Gardner,[17] in which 0.1 N HCl is employed to detect red cell panagglutinins at pH 6.5 in acquired hemolytic anemia. Citric acid has been utilized here for platelet agglutinins, because sodium chloride decreases the cataphoretic velocity of platelets and may induce spontaneous agglutination.[18] A final pH of 6.6 to 6.9 is obtained after the addition of platelet-rich plasma.

† We are indebted to Mr. Harold Ray, chief technologist, Bacteriology and Serology Laboratory, Barnes Hospital, for determining the anticomplementary activity.

Dextran and gelatin have been found to be unsatisfactory. Normal plasma and serum may be used after addition of Sequestrene and citric acid.

Slide testing anti-D serum caused prompt agglutination of D positive red cells collected in the manner described for platelets. Therefore, incomplete antibody is apparently detectable by the method outlined here and one other technic [14]; the remainder of those previously described [19, 20] were not designed for this purpose and only occasionally were performed in a manner which might detect incomplete antibody.

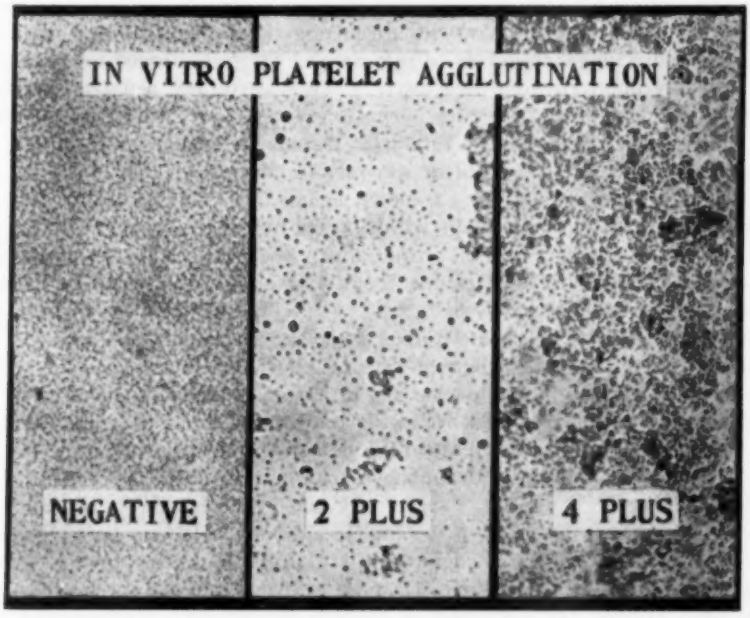

FIG. 1. Platelet agglutination as it appears at 100 × magnification. The degree of clumping is graded 1+ to 4+, as judged by both number and size of agglutinates, and number of unagglutinated platelets.

Nonspecific agglutination of platelets may be caused by unclean materials, poor or difficult venepunctures, and contaminated sera or plasmas. Rare red cells, white cells, droplets of silicone or neutral fat from lipemic plasmas do not interfere with the reading.

Other studies to be described required the preparation of anti-rat platelet serum. Blood was obtained by cardiac puncture from Wistar strain rats and pooled in 150 c.c. amounts in 3 per cent sodium citrate. The platelets were separated by differential centrifugation and washed three times in isotonic sodium chloride solution containing 0.3 per cent sodium citrate. The packed platelets were then resuspended in 6 c.c. of saline and kept refrig-

erated until used. One cubic centimeter of the suspensions was given intravenously at weekly intervals for five weeks to a rabbit of the New Zealand strain. Ten days following the last injection the rabbit was bled, serum was separated from the clotted blood and frozen at — 20° C. until needed. The phase microscopy technic of Brecher and Cronkite [21] was employed for platelet counts on rat tail blood.

II. Evidence for an Increased Rate of Platelet Destruction

The normal life span of circulating platelets is thought to be five to seven days,[22, 23, 24] and the "megakaryocyte ripening time" (i.e., the time required for immature megakaryocytes to mature and produce circulating platelets) is probably approximately five days.[25] Thereafter, any acute unsustained insult simultaneously affecting megakaryocytes and circulating platelets would be expected to cause a fulminant thrombocytopenia which would require approximately five days for recovery to take place.

In thrombocytopenia due to known agents [26] a "platelet crisis" [27] is induced in susceptible individuals within a few hours of administration of an offending drug, e.g., Sedormid or quinidine. In vitro studies have indicated that the low platelet level is due to an immunologic mechanism causing platelet agglutination and lysis.[28, 29, 30, 31, 32, 33] The antigen under these circumstances consists of a platelet-drug complex; the antibody is found in the patient's serum. An accelerated rate of platelet destruction is of major importance, therefore, in this variety of thrombocytopenia. Recovery usually occurs within one week following removal of the responsible agent.

Platelet agglutinins have also been demonstrated in vitro in the plasma of patients with idiopathic thrombocytopenic purpura, first by Evans [14] and later by others.[34, 35] Evans [14] specifically noted the desirability of designing his test to permit detection of incomplete antibody. In our series, plasmas from 31 patients with this disorder were studied in vitro by the technic described above. Twenty-one plasmas revealed circulating platelet agglutinins (figure 2). In addition, in vivo studies have demonstrated that most (but not all) patients with idiopathic thrombocytopenic purpura have a circulating thrombocytopenic factor.[15, 16, 36] When whole blood or plasma from patients with idiopathic thrombocytopenic purpura was transfused into normal recipients, a precipitous drop in the platelet count of the recipient occurred in 16 out of 26 instances (figure 3). At times the induced thrombocytopenia was associated with purpura and other clinical evidences of bleeding. The entire pattern of abnormal reactions of laboratory tests characteristic of thrombocytopenia was also noted: prolonged bleeding time, increased capillary fragility, decreased clot retraction, decreased prothrombin consumption, and morphologic changes in bone marrow megakaryocytes so that very little platelet formation could be seen. The depressed platelet level persisted for from four to seven days. Recovery was often characterized by a secondary thrombocytosis which lasted for several days. Red

cell counts did not change unless there was blood loss. White cell counts varied, but an initial leukopenia followed in one or two days by a moderate leukocytosis was commonly observed. The platelet-depressing constituent in the donor plasma is a globulin,[16] presumably identical to the in vitro

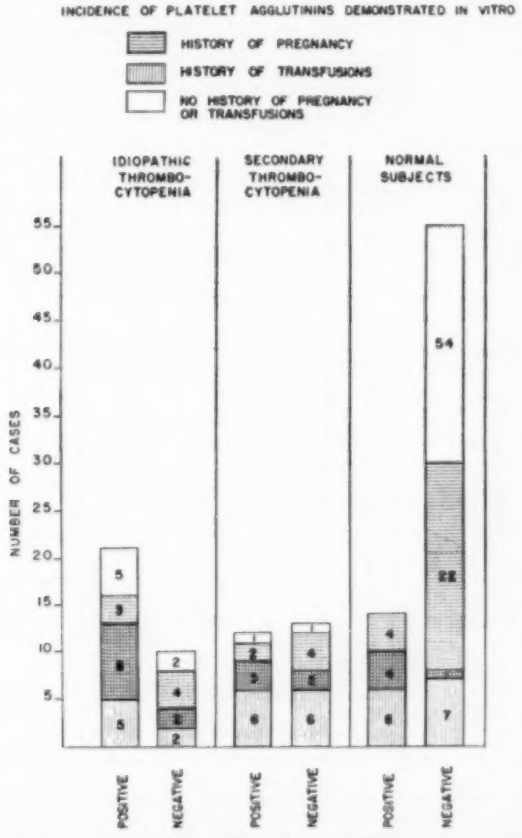

FIG. 2. The incidence of platelet agglutinins as demonstrated in vitro. Although agglutinins may develop as isoagglutinins in normal individuals following repeated transfusions or pregnancies, they may occur in idiopathic thrombocytopenia as autoagglutinins. However, many thrombocytopenic purpura patients have no agglutinins. The subjects designated as normal included a variety of disorders, e.g., refractory anemias, bleeding peptic ulcers, hereditary hemolytic syndromes, etc., in which there was no evidence of platelet disturbance.

platelet agglutinin, and presumably also capable of damaging megakaryocytes. In no instance has the in vitro test been negative when the in vivo test was positive. These in vivo observations have been corroborated [37, 38, 39, 34] and are remarkably similar to those obtained in animals by Ledingham,[40, 41]

Bedson,[42] Tocantins [43, 44, 45, 46] and others [47, 48, 49] in their classic experiments with heterologous antiplatelet sera.

A second type of in vivo evidence for a circulating thrombocytopenic factor has been obtained from observations in which the transfusions have been essentially reversed. Normal platelets transfused into patients whose

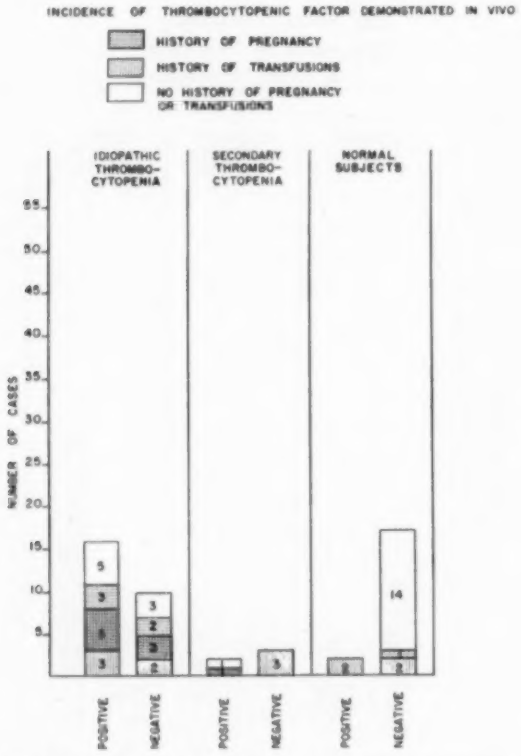

FIG. 3. The incidence of the thrombocytopenic factor as demonstrated in vivo. A low platelet count was induced in normal recipients of plasma from many patients with idiopathic thrombocytopenia, whether or not these patients had a history of pregnancy or multiple transfusions. Among normal individuals, only those who had received many transfusions had a circulating thrombocytopenic factor. The subjects designated as normal included a variety of disorders, e.g., refractory anemias, bleeding peptic ulcers, hereditary hemolytic syndromes, etc., in which there was no evidence of platelet disturbance.

thrombocytopenia was due to bone marrow aplasia remained in the circulating blood for from four to six days. However, when transfused into patients with idiopathic thrombocytopenic purpura, normal platelets could be detected for only a few hours.[50, 51, 52, 53, 36]

The following case is illustrative of the group in which a circulating thrombocytopenic factor has been demonstrated.

Case Report

Case 13. F. C., a nulliparous housewife, 46 years of age, was first admitted in August, 1950, because of petechiae, ecchymoses and epistaxes of one month's duration. Her platelet count at this time was 10,000 per mm.[3] Splenectomy was followed by only a transient, suboptimal increase in platelets to 120,000 per mm.[3] Within two weeks the pronounced thrombocytopenia recurred. Four transfusions of whole blood were given to her during this hospitalization. In October, 1950, transfusion of 500 c.c. of her whole blood to a normal recipient induced, within three hours, the entire clinical and laboratory syndrome of idiopathic thrombocytopenic purpura. The platelet count of the recipient was 800,000 per mm.[3] immediately prior to the transfusion, 400,000 15 minutes later, 125,000 after one hour and 25,000 per mm.[3] after two hours. The tourniquet test for capillary fragility was then noted to be positive, and the bone marrow, previously normal, now showed the changes seen in idiopathic thrombocytopenic purpura.[1-6, 54, 55, 56] The following day there were scattered petechiae on the lower extremities and a stool contained occult blood. An exchange transfusion of 2,000 c.c. did not alter the degree of thrombocytopenia. Recovery began on the fourth day and the platelet count attained a maximal level of 1,100,000 per mm.[3] on the eighth day (table 2).

Table II

Effect of Whole Blood from Patient F. C. on Normal Recipient

Date	Patient F. C.		Recipient W. H. Platelets $\times 10^3$ per mm.^{3}										
				After Transfusion of 500 c.c. of Patient's Whole Blood									
	Platelets $\times 10^3$ per mm.^{3}	Agglutinin Titer	Before Transfusion	15 Min.	1 Hr.	2 Hrs.	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	8 Days
10–22–50	0	1:16	800	400	125	25	0	15	35	117	260	320	675	1,100

Plasma from Patient F. C. contained agglutinins in vitro against all platelets tested.
Changes produced in the platelet count of a normal individual after transfusion of 500 c.c. of whole blood from patient F. C., whose plasma contained platelet agglutinins in a titer of 1:16 against the recipient's platelets.

These observations suggested that the thrombocytopenia in F. C. was due to an autoimmunologic mechanism. Cortisone was administered orally in a dose of 400 mg. daily for two days and 200 mg. daily for the next two weeks. A decrease in severity of her purpura was not associated with any change in her platelet count of zero, or in the effect of her plasma given intravenously to normal recipients. Furthermore, when her plasma was injected into a normal recipient who had been given ACTH (25 mg. intravenously every six hours) for one day preceding the transfusion, no inhibition of the thrombocytopenic effect was noted. Eighteen milligrams of nitrogen mustard (methyl-bis beta-chloroethyl amine hydrochloride) were given to the patient in an attempt to inhibit antibody formation,[57, 58] but an increase in severity of her bleeding manifestations developed. Transfusions of fresh, platelet rich polycythemic blood failed to increase her platelet count even momentarily[56]; also ineffective was blood from an individual who had previously been a recipient of her plasma. She was maintained for the subsequent 10 months on transfusions to replace blood continually being lost. In November, 1951, all bleeding stopped spontaneously, although her platelet count did not change significantly until June, 1952. She is now symptom-free, with a platelet count of 116,000 per mm.[3] Thorotrast studies have not revealed any accessory splenic tissue.[59]

The evidence which indicates that a circulating thrombocytopenic factor, presumably a platelet agglutinin, is of importance in the pathogenesis of many cases of idiopathic thrombocytopenic purpura may be summarized as follows:

1. Platelet agglutinins have been demonstrated in the plasma of patients with idiopathic thrombocytopenic purpura; 21 of 31 plasmas caused agglutination of platelets in vitro (figure 2).
2. Transfusion of 500 c.c. of whole blood or its plasma equivalent from 26 patients whose thrombocytopenia was of the idiopathic variety induced a rapid and sustained decrease in the recipients' circulating platelet level in 16 instances (figure 3). When the bone marrow was also studied, changes in the morphologic appearance of megakaryocytes were observed whenever thrombocytopenia was induced.
3. The survival time of transfused platelets was markedly shortened in many cases of idiopathic thrombocytopenic purpura.

These observations support the concept that an autoantibody which damages both megakaryocytes and platelets is frequently responsible for the low platelet count.

III. Platelet Autoagglutinins, Isoagglutinins and "Types"

The incidence of autoagglutinins for platelets in the plasma of the patients studied cannot be stated for various reasons. The first of these is that all of the in vivo and most of the in vitro data were obtained by testing for isoagglutinins (i.e., agglutinins for human platelets other than those of the patient). Although the incidence of naturally occurring isoagglutinins is apparently negligible as detected by the technics herein described, immune isoagglutinins were found in the plasmas of 14 normal individuals after repeated transfusions or pregnancies (figure 2). All but nine of the patients with idiopathic thrombocytopenic purpura either had received transfusions or had been pregnant. Of these nine, five had platelet agglutinins and four did not. (Two of the four were tested only in vivo prior to the development of a satisfactory in vitro test, and accordingly are not included in figure 2.) Eight additional patients had no demonstrable platelet agglutinins, even though they had been pregnant or had been transfused. In four other instances it was possible to demonstrate autoagglutinins in the patient's plasma for his own platelets. Accordingly, it was in only these 21 patients (nine who could not have been isoimmunized, eight others with no platelet agglutinins, and four in whom autoagglutinins were demonstrated) that the presence or absence of a platelet autoagglutinin mechanism could be identified.

Secondly, platelet autoagglutinins are not always panagglutinins (i.e., are not necessarily active against all platelets, despite a strong agglutinating effect against the patient's own platelets) under the limitations of the technics

herein employed. This fact was demonstrated in patients C. S., L. N., D. G. and M.H., whose plasma collected while they were thrombocytopenic agglutinated their own platelets obtained after recovery had occurred but did not agglutinate all other platelets tested (table 3).

There are also other circumstances under which platelet autoagglutinins are not panagglutinins. As pointed out previously, in purpura due to known agents a platelet-allergen complex is required for the antibody in the patient's plasma to cause agglutination. It appears likely that this mechanism is responsible for the thrombocytopenia in some cases designated as idiopathic, and that the allergen is not recognized. Under these circumstances the plasma would be expected to agglutinate only platelets similarly combined with an offending allergen. Additional evidence is obtained from the observation that transfusion of blood from a patient with purpura due to

TABLE III

Evidence That Platelet Autoagglutinins Are Not Panagglutinins

Plasmas Collected from:	Platelets from Individuals with Red Cell Group									
	ABO Rh	O +	O −	A +	A −	B +	B −	AB +	AB −	A* +*
Control subject		−	−	−	−	−	−	−	−	−
Patient L. N. during thrombocytopenia		−	−	−	+	+	+	+	+	+
Patient L. N. during remission (ACTH)		−	−	−	+	+	+	+	+	−

* L. N., platelets obtained during remission.

Data which illustrate that platelet autoagglutinins are not always panagglutinins. Plasma from patient L. N. obtained during her thrombocytopenia did not agglutinate all platelets tested, although it did agglutinate her own platelets. Her postremission plasma failed to agglutinate her own platelets, although it still agglutinated other platelets, probably as a consequence of isoimmunization from repeated transfusions.

Sedormid failed to alter the platelet count of a normal recipient who was not sensitive to Sedormid.[60]

A third reason for not being able to estimate the incidence of autoagglutinins for platelets among the patients studied is that information is only now being accumulated concerning the existence of serologically different platelet types. Patients who have frequently been transfused for anemia due to marrow aplasia sometimes have strikingly rapid disappearance of transfused platelets,[26] a phenomenon whose evolution has been noted during successive platelet transfusions.[51, 61] Immunization apparently occurs independently of ABO and Rh compatibility of red cells. Furthermore, transfusions of whole blood or plasma from donors who have repeatedly received blood for any reason can induce severe thrombocytopenia in normal recipients (figure 3).[26]

The evidence for immunologic differences in platelets from different individuals has stimulated an investigation into the feasibility of typing

platelets. The "typing sera" consist of plasma obtained from patients repeatedly transfused for refractory anemia. The data obtained thus far do not permit any accurate estimate of the number or incidence of different platelet types, although eight serologically distinct ones have been identified. The approximate incidence of only one of these types (Type I, table 4) has been established by both in vitro agglutination and agglutinin-absorption technics. Among the first 110 consecutive persons tested, 18 per cent were found to have the same platelet type by both methods. Table 4 contains data obtained on 40 of these individuals collected on the basis of their availability for repeated study over a period of many months. Additional evidence for antigenic differences in platelets was obtained by immunization of a normal Type III recipient with weekly transfusions of 50 c.c. volumes of Type I whole blood collected in a siliconed syringe. After five weeks the Type III individual had definite isoagglutinins against platelets from individuals belonging to Type I.

TABLE IV

Incidence of Platelet Types

Platelets	Sera											Per Cent Incidence
	Control	1	2	3	4	5	6	7	8	9	10	
I	−	+	+	+	+	+	+	+	−	+	+	18%
II	−	−	−	−	−	−	−	−	−	−	−	20%
III	−	−	−	−	−	−	−	−	−	−	+	18%
IV	−	−	+	−	−	−	−	−	−	−	+	10%
V	−	−	+	−	+	−	−	−	−	−	+	8%
VI	−	−	+	+	−	−	−	−	+	−	+	5%
VII	−	−	−	−	−	−	−	−	+	−	+	5%
VIII	−	Five miscellaneous groups, each less than 5%										16%

The incidence of different platelet types among the 40 individuals repeatedly tested against 10 "platelet-typing sera."

Only Type I has been established by both agglutination and agglutinin absorption technics. Serum No. 8 was obtained by absorption of isoagglutinin on a Type I platelet suspension.

Figure 2 summarizes the data for platelet agglutinins demonstrated by in vitro testing. The majority of the cases of symptomatic thrombocytopenia were due to marrow replacement or aplasia. There were the following exceptions: three patients with disseminated lupus erythematosus (one positive), one infant with an extensive hemangioma of the thigh (negative), one case of postvaccinial thrombocytopenia in a child (negative), one patient with congestive splenomegaly (negative), and one man with disseminated miliary granulomas of undetermined etiology in the spleen (negative). Worthy of note are: (1) the frequency of isoagglutinins for platelets in any individual with a history of transfusions or pregnancy; of 26 parous women tested, four multiparas had strong platelet agglutinins for some platelet suspensions; (2) the absence of platelet isoagglutinins in normals who lack such a history, and (3) the spontaneous occurrence of agglutinins in patients with idiopathic thrombocytopenic purpura.

IV. Idiopathic Thrombocytopenic Purpura Without Evidence of Platelet Destruction

Fourteen patients, seven of whom were classified as having acute thrombocytopenia, had no demonstrable platelet agglutinins by the in vivo or in vitro technics employed. An increased rate of platelet destruction cannot be excluded in all these patients. In at least one instance, however (case 21), normal survival of transfused platelets was observed.[36] This observation suggests that decreased rate of formation of circulating platelets from megakaryocytes may be the sole mechanism responsible for some cases of idiopathic thrombocytopenic purpura. There are no obvious clinical features which distinguish this group of patients from that in which platelet agglutinins were identified. However, they did not seem to respond so well to splenectomy. Eleven patients in whom platelet agglutinins were not demonstrable had their spleens removed. Only one had a complete remis-

Table V

Apparent Variation in Response to Splenectomy

Platelet Agglutinins	Number of Cases			
	Degree of Response			
	None	Doubtful	Incomplete	Complete
Not demonstrable	6	2*	2	1
Demonstrable	6		1	11

* Recovery probably attributable to parturition.

A tentative breakdown of the 29 cases treated by splenectomy. Because of the current limitations in detecting platelet autoagglutinins, and the numerical inadequacy of the series studied, these data can be presented as merely suggesting a variability in response to splenectomy. Patients without platelet agglutinins appear to respond less frequently than those with agglutinins.

sion. Two experienced suboptimal increases in their platelet counts. One was pregnant at the time of splenectomy and developed a lasting remission only after delivery. In another pregnant patient, an incomplete remission followed combined splenectomy and Cesarean section. The remaining six were not benefited by removal of their spleens. In contrast to this, of 18 patients with platelet agglutinins who were treated by splenectomy, 11 had complete remissions, one had only a suboptimal increase in her platelet count, and six were not benefited (table 5).

The following case is illustrative of thrombocytopenia without circulating platelet agglutinins.

Case 32. J. B., a merchant 62 years of age, was studied in March, 1951, at which time his idiopathic thrombocytopenic purpura was of 10 months' duration. His illness was characterized by petechiae, ecchymoses and intermittent, severe gastrointestinal bleeding. Twenty-one transfusions had been required during this period, which

were usually followed by a decrease in severity of bleeding manifestations for from four to six days. Transfusion of 330 c.c. of his plasma failed to alter the platelet count of a normal recipient (table 6), and agglutinins were not demonstrable in vitro against the 17 platelet suspensions tested. Cortisone given orally in a dosage of 300 mg. the first day, 200 mg. the second day and 100 mg. daily for the next 10 days produced no platelet response. Splenectomy was likewise without beneficial effect during a 12 week period of observation.

The evidence for a type of idiopathic thrombocytopenia due solely to a decrease in platelet formation from megakaryocytes is less convincing than that for thrombocytopenia due to increased platelet destruction. However, differences to be described between the newborn of mothers who have idiopathic thrombocytopenic purpura with platelet agglutinins and those who do not have the plasma factor support the concept. Also, the observation

TABLE VI

Data Illustrating the Failure of Transfusion of Plasma from a Patient without Platelet Agglutinins to Alter the Platelet Count of a Normal Recipient

Date	Patient J. B.		Recipient L. A. Platelets $\times 10^3$ per mm.^{3}				
	Platelets $\times 10^3$ per mm.^{3}	Agglutinin Titer	Before Transfusion	After Transfusion of 330 c.c. Patient's Plasma			
				1 Hour	3 Hours	1 Day	2 Days
3-11-51	8	Negative	446	441	427	392	463

Plasma from Patient J. B. contained no agglutinins in vitro against any platelets tested.

that lasting remission may follow transfusion of blood from a donor with thrombocytosis [53] suggests that in some instances deficiency of a megakaryocyte maturation factor may be responsible for the low platelet count. Patient I. B. (case 21), who had been thrombocytopenic for two months, appeared to respond to a transfusion of platelet-rich whole blood with a remission one week later.

V. The Rôle of the Spleen

There is general agreement that the spleen is somehow involved in the pathogenesis of idiopathic thrombocytopenic purpura, as the high remission rate following splenectomy is difficult to explain on any other basis. Difference of opinion exists, however, as to its exact rôle: whether it inhibits platelet production or removes circulating platelets at an excessively rapid rate. Evidence for the latter rôle has been obtained.

The first and most significant observation is that splenectomized animals are less susceptible to the action of heterologous anti-platelet serum than are paired normal litter mates. Although a sufficiently large dose of serum will cause thrombocytopenia in both normal and splenectomized rats, smaller doses will induce a rapid disappearance of circulating platelets in only the

intact animal (figure 4). Previous investigators using guinea pigs and rabbits [62, 48] attributed the protective effect of splenectomy to the higher platelet count in the splenectomized animals. However, the data presented in figure 4 are representative of observations made on 14 rats splenectomized two months prior to this study, whose platelet counts had stabilized at normal levels. Under the conditions of this experiment it seems reasonable to assume that the spleen is an important site for the mechanical removal of antibody-coated platelets. A similar phenomenon was observed in several human subjects (figure 5). Transfusion of potent thrombocytopenic plasma caused fulminant, sustained thrombocytopenia in both normal and splenec-

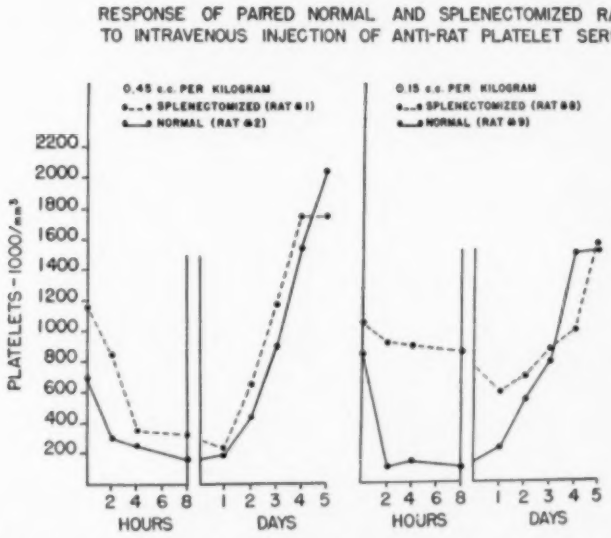

FIG. 4. Observations which indicate that splenectomized rats are less susceptible to heterologous anti-rat platelet serum than are their paired normal litter mates. Although a large dose of serum will induce similar degrees of thrombocytopenia in both groups of animals, smaller doses affect the platelet count in only the intact animals. Intravenous injections of anti-platelet serum were given at 0 time.

tomized recipients. Transfusions of relatively less potent thrombocytopenic plasma induced a low platelet count in only the recipient whose spleen had not been removed.

These observations suggest that (1) the spleen removes sensitized platelets, but (2) if the platelet antibody titer is high, platelet destruction occurs even in the absence of the spleen. They also provide a possible explanation for the failure of splenectomy to induce a remission in every patient, since high concentration of the antibody would cause continued abnormal removal of platelets even after splenectomy. Because the titer of platelet agglutinins was not being measured when most of these patients were being studied, the

data are not available to determine whether therapeutic failures could be explained on the above basis. Six out of 18 patients with platelet agglutinins in their plasma failed, however, to respond to splenectomy. Platelet agglutinins persisted in the plasma of all six. When platelet agglutinins were found after splenectomy-induced remissions,[16, 36] their concentration was presumably too low to cause removal of platelets from the circulation in the absence of the unique circulatory bed of the spleen.

If the evidence is valid that the spleen is an important source of antibody,[63, 64, 65] then its removal would reduce production of platelet agglutinin

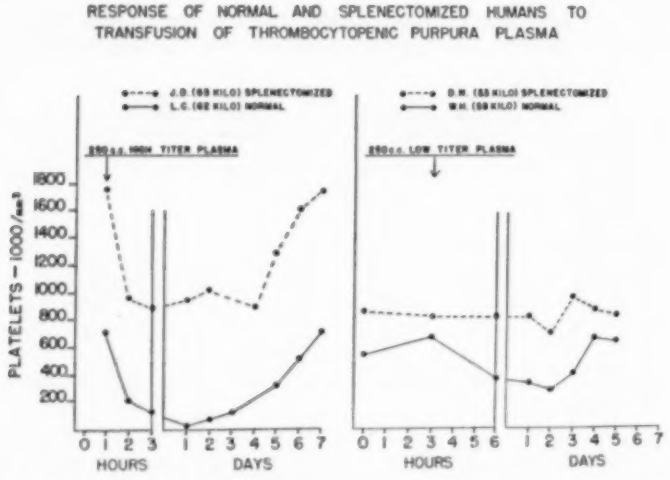

FIG. 5. The results of studies on the response of normal and splenectomized humans to transfusions of potent and relatively less potent plasma from donors with idiopathic thrombocytopenic purpura. Thrombocytopenia was induced in non-splenectomized recipients on all occasions, but in the splenectomized individuals by only the potent plasma. The scale is so constructed that the platelet count of the normal recipient of less potent plasma does not appear to have decreased significantly. The platelets decreased, however, from a pre-transfusion level of 655,000 per mm.³ to 305,000 per mm.³ an unequivocal effect.

and assist in inducing a remission. The following case illustrates these effects of splenectomy in a thrombocytopenic patient with platelet agglutinins.

Case 4. C. S., a woman 46 years of age, was admitted in April, 1952, with a history of two prior episodes of purpura, one 10 years and one four months previously. There had been a recurrence seven weeks preceding admission. She had never been transfused or pregnant. Transfusion of her plasma into a normal recipient caused a significant, sustained decrease in his platelet count. Splenectomy was accomplished without administration of blood. (Five per cent glucose in water, saline, and 100 c.c. of 25 per cent serum albumin were employed.) Prompt remission occurred, although 10 days later a mild thrombocytopenic effect of her plasma was again demonstrated in the same recipient. One month later no such plasma effect was demonstrable. These data are compiled in table *7*.

Lack of agreement concerning the exact rôle of the spleen has been due largely to difference in results obtained when platelet counts were performed simultaneously on splenic venous and arterial blood. Some investigators have found significantly lower levels in the venous blood,[66, 67, 68, 69, 10, 11] whereas others have been unable to confirm that observation.[69, 70, 71, 72, 73] The discrepancy may be attributable to a variable rôle of the spleen in different patients with idiopathic thrombocytopenia and also to the limitations inherent in technics of platelet sampling and counting. Significant differences in the two platelet counts would be meaningful, but since in any one circulation through the spleen only a small percentage of the total number of platelets may be removed, failure to observe a lower level in splenic venous blood would not necessarily exclude splenic sequestration of these

TABLE VII

Changes in Tests on Patient C. S. Following Splenectomy

Date	Patient C. S.		Recipient W. H. Platelets × 10^3 per mm.^{3}								
	Platelet × 10^3 per mm.^{3}	Agglutinin Titer	Before Transfusions		After Transfusions of 300 c.c. of Patient's Plasma						
			3 Hours	0 Time	3 Hours	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days
4-14-52	0	1:32	680	700	465	450	240	265	720		
Splenectomy											
4-25-52	1,722	1:8	575	655	370	346	305	409	670		
5-27-52	1,251	Negative	429	455	400	693		465	493	474	585

Autoagglutinins were demonstrated for patient's platelets on April 14 and April 25 but not on May 27, 1952.

Observations on the effect in vitro and in vivo of the plasma of patient C. S. obtained prior to and 10 days and one month following splenectomy. The patient's platelet count promptly rose to supernormal levels, but both the in vitro agglutinins and the in vivo thrombocytopenic effect disappeared only gradually.

elements. Interpretations of data from studies of pulmonary removal of platelets may similarly be questioned.[74]

Among the 14 patients in whom evidence for increased platelet destruction was lacking, 11 were treated by splenectomy. Only one had a good response, and two were briefly, suboptimally benefited. The evidence is insufficient to attribute the single good response to enhancement of bone marrow function because of splenectomy or to the physiologic effects of surgical stress. As previously mentioned, two other patients improved immediately postpartum, possibly as a consequence of parturition. One of the patients had failed to obtain a lasting remission following splenectomy early in pregnancy. The other was splenectomized at term and delivered by Cesarean section.

The data available, although suggesting that the spleen functions by removing sensitized platelets, do not exclude the possibility that splenic

inhibition of bone marrow megakaryocytes is of importance.[2-6] Recent physiologic studies which have demonstrated that splenectomy may be followed by increased erythrocytopoiesis [75] make more tenable the belief that thrombocytopoiesis may be similarly affected.

V. Effect of ACTH and Cortisone

In contrast to the frequent persistence of circulating platelet agglutinins after remission induced by splenectomy, remissions produced by ACTH or cortisone therapy seem to be associated with disappearance of the ag-

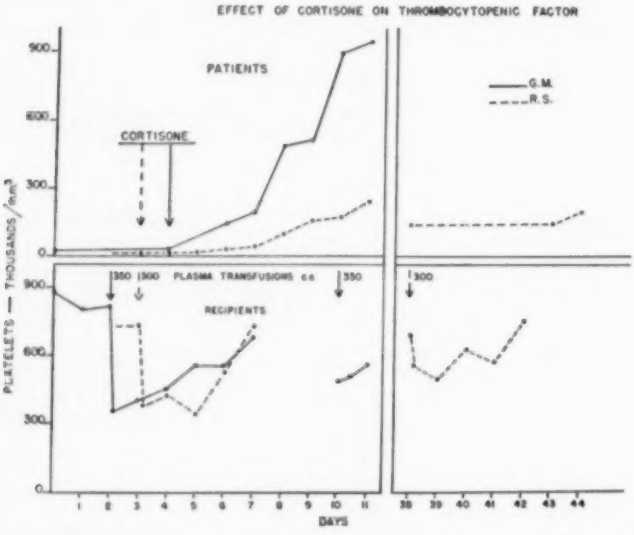

Fig. 6. Data on the effect of cortisone in two patients with idiopathic thrombocytopenia. Both received a similar daily dosage initially (200 mg.), and it was continued in 100 mg. dosage in both until the second plasma samples were obtained. The observations indicate that a complete remission from cortisone is associated with disappearance of the thrombocytopenic factor, and suggest that an incomplete remission is attended by only a partial loss of plasma potency. Patient R. S. later responded promptly to splenectomy.

glutinin.[16, 36] If it fails to disappear the platelet count persists at a low level or rises only slightly (figure 6). Collateral evidence for this rôle of adrenal cortical hormones has been obtained from animal experiments in which the administration of cortisone does not alter the thrombocytopenia induced in rats by the injection of heterologous antiplatelet serum.[76] Two patients in whose plasma platelet agglutinins could not be detected appeared to respond to adrenal cortical hormones (figure 7). Presumably the latter agents stimulated an increased rate of formation of circulating platelets. Until isotopic or other technics are available for evaluating the rate of platelet

production and turnover, these effects of ACTH and cortisone cannot be established.

Decreased severity of purpura without an associated increase in platelet count [77, 78, 79] has been noted in a few instances.

VII. Mechanism of Spontaneous Remission

One patient, C. D., whose plasma contained platelet agglutinins detected by both in vivo and in vitro technics while he was thrombocytopenic, demonstrated neither phenomenon after spontaneous remission.[36] No data are

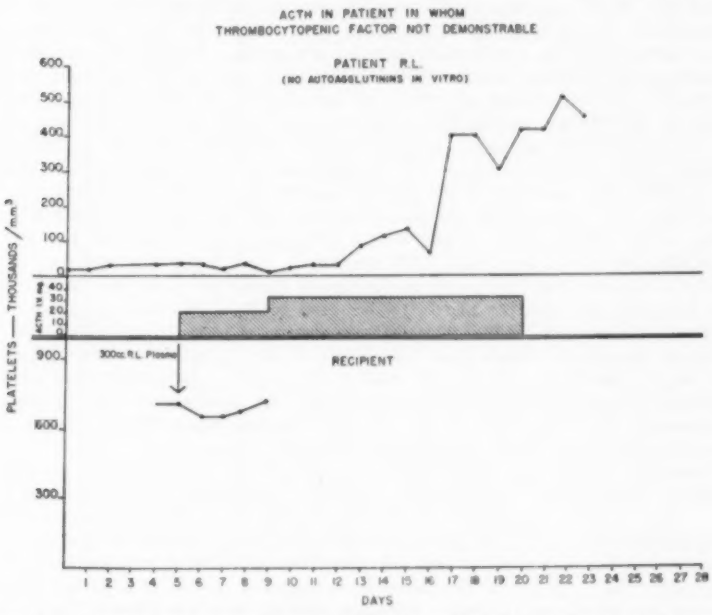

Fig. 7. A representative response to ACTH by patient R. L. On all four occasions on which she has been treated with ACTH her platelets have increased to normal levels within 10 days to two weeks. She has no autoagglutinins in vitro and no thrombocytopenic factor demonstrable by in vivo studies.

available concerning the mechanism of spontaneous remission in patients whose plasma has no platelet agglutinating effect, although one patient (R. L.), who had several spontaneous remissions, on one occasion recovered following an exploratory laparotomy, at other times seemed to respond to ACTH (figure 7).

VIII. Neonatal Thrombocytopenia

The literature on neonatal thrombocytopenia has been recently reviewed and evidence has been presented to indicate that "transplacental passage of

some factor,"[80] possibly an "immune body" or a "hormone,"[81] is responsible for its pathogenesis. The technics described above were applied to a study of seven women who had had a combined total of 12 pregnancies in which either the mothers or the babies had purpura (table 8).

Three of the mothers had platelet agglutinins in their plasma, although two had normal platelet levels following splenectomy and the third had obtained moderate improvement from this procedure. All eight infants born to these three mothers had thrombocytopenic purpura. They illustrate one variety of neonatal thrombocytopenia.

Case 25. M. H., a housewife 31 years of age, was first hospitalized in June, 1938, with complaints of easy bruising for six years, menorrhagia for three years, recurrent epistaxes for six months, and menorrhagia for six weeks. A diagnosis of idiopathic thrombocytopenic purpura was made and splenectomy was performed, with a good initial result. Her platelet count, which had been 1,000 per mm.^{3} prior to operation, increased to 200,000 the first postoperative day and to 600,000 per mm.^{3} seven days later. Twelve transfusions were given during this hospitalization and an additional 12 during subsequent admissions. The patient was not seen again until January, 1941, at which time she was in the seventh month of her first pregnancy. In the interval since her splenectomy she had been well but for the recurrence of easy bruising. Her platelet count on the second admission was 87,000 and two months later, at the time of delivery, was 8,000 per mm.^{3} One week after delivery it had gradually increased to 490,000, only to decline to 36,000 per mm.^{3} two weeks later. On the few occasions that her platelets have been counted between pregnancies they have been in the range of 15,000 to 50,000 per mm.^{3} At term in her subsequent four pregnancies, the platelet counts have been 36,000, 7,000, 0, and 0 per mm.^{3} Purpura, of mild degree, has been present only during pregnancies. Deliveries have all been accomplished spontaneously at term, and on only one occasion (fourth pregnancy) has postpartum blood loss been excessive. In 1946 Thorotrast studies, and in 1949 abdominal arteriography, failed to reveal an accessory spleen.

Transfusion studies performed with this patient's plasma are shown in table 9. Her plasma was tested in vitro against 60 platelet suspensions and agglutinated 23 of these. In addition, autoagglutinins were demonstrable in vitro for her own platelets, and her plasma agglutinated the platelets of all four of her children so tested.

The patient has been married twice; her first husband died shortly before the birth of their first child. All five of her babies have appeared normal at birth but within a few hours have developed purpura. Pertinent data on each are given in table 8.

Once the platelets began to increase, in each case they rose from an average level of approximately 10,000 to supernormal levels in one to two weeks. Babies two and three were followed until platelet counts of 982,000 and 1,645,000 per mm.^{3} were attained.

Case 24. B. T., a housewife 23 years of age, had a diagnosis of idiopathic thrombocytopenic purpura made when she was 10 years old. Her complaints consisted of easy bruising and epistaxes for the previous four years. At the age of 16, her bleeding manifestations became milder, and during her first pregnancy two years later they were minimal. No transfusions had ever been required. In June, 1947, she delivered spontaneously at term. A platelet count during labor was 165,000 per mm.^{3} and there was no excessive postpartum blood loss. During the next five weeks her platelet count ranged from 71,000 to 149,000 per mm.^{3} Splenectomy was therefore performed in August, 1947, at which time she received 500 c.c. of whole blood. Thrombocytosis rapidly followed, her platelet count on the third and fifth postoperative days, respectively, being 1,600,000 and 2,800,000 per mm.^{3} There has been no further

TABLE VIII

Thrombocytopenia in Pregnancy and in the Newborn

Case No.	Mother								Baby									
	Name	Parity	History of Transfusions	Purpura		Tests*			Baby	Date	Sex	Platelet Count at Birth	Duration of Thrombocytopenia	Symptoms and Signs	Therapy†	Outcome	In Vitro Tests*	
				Present	Past	In Vivo	In Vitro											
							All Platelets	Some Platelets									All Platelets	Some Platelets
I. Mother and Baby Both Affected																		
25	M. H.	5	+	+	+	+	−	+	1	3- 7-41	F	zero	11 weeks	Petechiae, ecchymoses, gross and occult blood in stools.	4 transfusions	Complete recovery	0	0
									2	4-24-45	F	zero	7 weeks	Petechiae, occult blood in stools.	2 transfusions	Complete recovery	0	0
									3	8-21-46	F	zero	9 weeks	Petechiae.	5 transfusions	Complete recovery	0	0
									4	9-10-49	M	zero	12 weeks	Petechiae, ecchymoses, occult blood in stools.	5 transfusions	Complete recovery	0	0
									5	10- 4-50	F	17,000	9 weeks	Petechiae, ecchymoses, occult blood in stools.	None	Complete recovery	0	0
24	B. T.	2	+	−	+	0	+	+	1	6-27-47	F	zero	12 weeks	Petechiae, ecchymoses, hematuria.	4 transfusions	Complete recovery	0	0
									2	7-20-48	F	20,000	11 weeks	None.	None	Complete recovery	0	0
8	L. P.	1	+	−	+	+	+	+	1	10- 7-51	F	18,000	4 days	Petechiae.	None	Complete recovery	0	+

TABLE VIII—*Continued*

Case No.	Mother								Baby									
	Name	Parity	History of Transfusions	Purpura		Tests*			Baby	Date	Sex	Platelet Count at Birth	Duration of Thrombocytopenia	Symptoms and Signs	Therapy†	Outcome	In Vitro Tests*	
				Present	Past	In Vivo	In Vitro										All Platelets	Some Platelets
							All Platelets	Some Platelets										
II. Baby Alone Affected																		
36	E. M.	3	−	−	−	0	+	+	3	2-14-49	F	8,000	2 weeks	Convulsions, petechiae, ecchymoses.	None	Complete recovery	−	±
37	M. B.	2	+	−	−	0	+	+	2	3-27-52	M	Rare	8 weeks	Petechiae, ecchymoses, gastrointestinal bleeding.	Transfusions	Complete recovery	−	+
III. Mother Alone Affected																		
19	S. H.	3	+	+	+	−	−	−	3	5-17-51	M	268,000					−	−
18	L. J.	2	−	+	−	0	−	−	2	3-20-52	M	270,000					0	0

* 0 = Tests not done; + = Positive results; − = Negative results.

† Transfusions averaged 60 c.c.

Data on patients with thrombocytopenia in pregnancy or in the neonatal period. On the basis of these 12 pregnancies in seven women, it is proposed that the mother and baby may both have thrombocytopenia if there are maternal autoagglutinins for platelets, that only the infant is affected if isoagglutinins are present, and only the mother has purpura if no immunologic mechanism is demonstrable.

TABLE IX

Demonstration of a Thrombocytopenic Factor, Presumably a Platelet Agglutinin, in the Blood of Patient M. H., Mother of Five Thrombocytopenic Infants

Date	Patient M. H.		Recipient L. C. Platelets × 10^3 per mm.^{3}									
	Platelets × 10^3 per mm.^{3}	Platelet Agglutinins*	Before Transfusion	After Transfusion of 500 c.c. of Patient's Blood								
			6 Hrs.	0 Time	3 Hrs.	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	8 Days
1-24-51	47	Not tested against L. C.	605	650	145	150	143	160	143	129	310	416	615

Autoagglutinins demonstrated in vitro for M. H. platelets.
* Positive against 23 out of 60 platelet suspensions subsequently tested.

thrombocytopenia or purpura. A platelet count done at the time of her second delivery, July 20, 1948, was 620,000, and her most recent count, in April, 1952, was 610,000 per mm.^{3}

This woman's plasma was added to 12 different platelet suspensions and strongly agglutinated all of them. Both of her babies had neonatal thrombocytopenia. The data on these are given in table 8.

Case 8. L. P., a primipara 19 years of age, was first seen in August, 1951, at which time she was in the sixth month of pregnancy. Her complaints consisted of petechiae, hematuria and bleeding gums of two weeks' duration. ACTH intravenously, 20 mg. daily over an eight hour period, was associated with a gradual increase in the platelet level from zero, initially, to 76,000 per mm.^{3} after eight days. It then decreased again, however, and gastrointestinal bleeding developed. Splenectomy was followed promptly by a remission. One thousand cubic centimeters of blood were administered during the operation.

Transfusion studies were performed on the day of admission. The effect of her plasma on a normal recipient's platelet count is shown in table 10.

In vitro studies revealed platelet agglutinins against the 13 platelet suspensions with which her plasma was tested.

In October she was re-admitted and delivered of a baby girl. Petechiae were noted over the scalp and arms of the infant, whose platelet count was 18,000 per mm.^{3} The mother's count at this time was 1,235,000 per mm.^{3} Only one test could be performed with the baby's serum, which likewise revealed platelet agglutinins. Data on the baby are given in table 8.

TABLE X

Evidence for a Platelet Agglutinin in the Plasma of Patient L. P., Who Subsequently Responded to Splenectomy But Later Delivered a Thrombocytopenic Infant

Date	Patient L. P.		Recipient W. H. Platelets × 10^3 per mm.^{3}							
	Platelets × 10^3 per mm.^{3}	Platelet Agglutinins	Before Transfusion	After Transfusion of 300 c.c. of Patient's Plasma						
				5 Hrs.	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days
7-27-51	2	Positive	725	410	420		425	513	586	760

It is postulated that the babies of these three mothers had neonatal thrombocytopenia because of transfer across the placenta of maternal autoagglutinins for platelets. It is true that isoimmunization to platelets could have occurred from whole blood transfusions, except for the first baby of mother B. T. Neonatal thrombocytopenic purpura is rarely seen in infants born to mothers who have never had thrombocytopenia, despite the frequency of pregnancy in women who have been transfused. Therefore, it seems more reasonable to attribute the low platelet counts at birth in these eight babies to the postulated mechanism of placental transmission of maternal autoagglutinins. The duration of the thrombocytopenia in the infants of M. H. and B. T. is of interest because of the much shorter course of the thrombocytopenia induced in normal adults in the in vivo studies previously described. This may be attributable to persistence of platelet agglutinins for many weeks in the plasma of the newborn, as has been established for red cell agglutinins in hemolytic disease of the newborn due to Rh incompatibility.[82, 83] Lozner, who for many years has been interested in the problem of congenital thrombocytopenia, is particularly impressed with the persistence of a low platelet count for an extended period of time in most cases of this disorder.[84]

An unusual variety of idiopathic thrombocytopenia of the newborn, which has been designated "primary thrombocytopenia," [85] occurs without concomitant maternal thrombocytopenia or without a prior episode of this disorder which had been treated by splenectomy. In this variety, mothers who are in an apparently perfect state of health may occasionally give birth to infants with thrombocytopenic purpura. It is suggested that this syndrome may develop because of placental transfer of maternal isoagglutinins for platelets developed as a consequence of prior pregnancies with fetal and maternal platelet incompatibilities. Data to support the hypothesis have been obtained in two instances.

Case 36. J. M.,* a white female infant, appeared normal at birth in February, 1949. She had a convulsion the following day, however, and petechiae and ecchymoses were then noted. She was seen at this time by Dr. William C. Moloney, who established the diagnosis of neonatal thrombocytopenia. There was no evidence of any infection or metabolic disease to account for the low platelet count. Pertinent data on the baby are shown in table 8.

The mother was 38 years of age and in good health. Three previous pregnancies had been uneventful, and her current delivery had been accomplished without difficulty but for midforceps instrumentation. She had never been given any transfusions and did not have thrombocytopenia. Both the mother and baby had the same red cell type: O, Rh positive. There was no agglutination of the infant's red cells in albumin when tested against her mother's serum.

The mother's plasma caused agglutination of her baby's and of all six other platelet suspensions to which it was added, but caused no agglutination of her own platelets. Only equivocal agglutination of one platelet suspension was caused by the child's plasma when studied in February, 1952.

* Arrangements to study this patient and her mother were kindly made by Dr. William C. Moloney, The Boston City Hospital, Boston, Massachusetts.

Case 37. M. B.,* a white male infant, was first noted to have thrombocytopenia 14 hours after birth. There was no evidence of sepsis, syphilis or metabolic disease to account for the low platelet count. Two bone marrow examinations showed an adequate cellularity, with many megakaryocytes. Only a rare, abnormal platelet could be seen in the peripheral blood. Recovery occurred after two months.

This had been the mother's second pregnancy, the first having been in 1948. Both deliveries were accomplished by Cesarean section because of cephalopelvic disproportion. During the first of these the mother had received two transfusions. She did not have thrombocytopenia.

The red cell phenotypes of M. B. and his father were identical: Group B, CDe, MN. His mother's red cells were Group O, CDe, N.

Sera from the patient and both of his parents were added to 13 different platelet suspensions (table 8). The mother had platelet agglutinins for all of these, the baby for seven and the father for two. It was not possible to test either the mother's serum or the patient's serum from the thrombocytopenic phase against his platelets after remission.

It appears certain that both of these mothers were isoimmunized to platelets through pregnancy alone in one instance, and pregnancy or transfusions in the other. Reference has already been made to the evidence that such isoimmunization can occur by either means. Isoagglutinins in the maternal serum for the child's platelets were demonstrated in one case. Although it has not been possible to perform the critical experiment, to demonstrate agglutinins in an infant's pre-remission serum for his post-remission platelets, nevertheless the presence of isoagglutinins in the sera of both newborn infants makes it likely that they were there as a consequence of maternal transmission and were active against the newborn's platelets. In addition to the obvious similarities between this mechanism and that which is well established for hemolytic disease of the newborn due to Rh incompatibility, it should be pointed out that thrombocytopenia has been noted in some cases of the latter.[86] Concomitant red cell and platelet isoimmunization may therefore occur.

Further evidence in support of the theory that a variety of neonatal thrombocytopenia may be caused by maternal isoimmunization to fetal platelets is derived from the observations of Goldstein,[87] who studied the blood of fraternal twins born to a mother with no history of purpura. One infant had thrombocytopenic purpura with a platelet count of 63,000. His sister had a platelet count of 158,000 per mm.^{3} and no evidence of bleeding tendency. The mother had 182,400 platelets per mm.^{3} probably a normal postpartum value, although the author considered it subnormal.

An attempt was made to reproduce in rats the phenomenon of neonatal thrombocytopenia. Rabbit anti-rat platelet serum was administered to pregnant female rats a few hours before delivery. This was unsuccessful; despite severe purpura in the mothers, the offspring were normal. Apparently the heterologous platelet antibody did not pass the placental barrier.

Another experiment was then carried out. Platelets from six Wistar

* Permission to refer to this case was kindly given by Dr. Nathan Smith, St. Christopher's Hospital for Children, Philadelphia, by whom the sera were supplied for this study.

strain albino rats and six black hooded rats were pooled separately. Three females of each strain were then injected intramuscularly with the pooled platelets obtained from the other strain. Injections were given twice weekly for three weeks. The black hooded females were then mated with an albino male, and the albino females were mated with a black hooded male. No significant differences were noted in the platelet counts of the newborn of either species, though they suckled "immunized" mothers. However, no platelet isoagglutinins were demonstrable in the maternal circulation. No further attempts have yet been made to reproduce in animals the syndrome of neonatal thrombocytopenia due to maternal isoagglutinins for fetal platelets, although further studies along these lines are warranted because of the studies of Young et al.,[88] who were able to produce hemolytic disease of the newborn in pups, provided they suckled an immunized dam.

Two mothers had severe thrombocytopenic purpura at the time of delivery but had no platelet agglutinins in their plasma. The infants in both instances were normal.

TABLE XI

Data Which Illustrate the Lack of Effect on a Recipient's Platelets of 500 c.c. of Plasma from Patient S. H., Whose Thrombocytopenia Was Apparently Not Associated with Circulating Platelet Agglutinins. Although Purpuric Herself, She Subsequently Delivered a Normal Infant

Date	Patient S. H.		Recipient E. B. Platelets × 10^3 per mm.^{3}				
	Platelets × 10^3 per mm.^{3}	Platelet Agglutinins	Before Transfusion		After Transfusion of 500 c.c. of Patient's Plasma		
			2 Days	0 Time	2 Hours	1 Day	4 Days
3-19-51	4	Negative	1,485	1,551	1,330	1,400	1,255

Case 19. S. H., a gravida three housewife 19 years of age, was admitted in March, 1951, because of gastrointestinal, vaginal and nasal bleeding of one month's duration. She was in the sixth month of her third pregnancy at this time. Her platelet count of 2,000 per mm.^{3} was not altered by six transfusions. Transfusion of 500 c.c. of her plasma failed to alter the platelet count of a normal recipient (table 11).

Splenectomy was followed by a one week period during which there was no response, and eight additional transfusions of whole blood were required, after which her platelets gradually increased to 221,000 per mm.^{3} over the following seven days. She was not seen again until she entered the hospital for delivery two months later. She had experienced recurrent bleeding for several days, and her platelet count was 30,000 per mm.^{3} Cortisone therapy was instituted but the delivery took place a few hours later. Her platelets promptly rose to normal thereafter. The baby showed no purpura and had a platelet count of 268,000 at birth and 400,000 per mm.^{3} three weeks later (table 8).

Case 18. L. J.,* a gravida three housewife 36 years of age, was admitted in March, 1952, in her ninth month of pregnancy. She gave a history of epistaxes, petechiae and ecchymoses of two weeks' duration. Blood obtained on entry showed

* We are indebted to Dr. Harry Agress, for permitting us to study this patient's serum. The surgery was performed by Dr. Sam Schneider and Dr. Seymour Monat.

no platelet agglutinins in vitro against the six platelet suspensions with which it was tested. Her treatment consisted of simultaneous Cesarean section and splenectomy. Excessive oozing and bleeding were encountered during the procedure, but her hospital course thereafter was uneventful. Her initial platelet count was 89,000 per mm.^{3} A suboptimal rise occurred following splenectomy, and although she has remained symptom-free a platelet count in June was still sub-normal at 143,000 per mm.^{3}

The baby was entirely normal, and at no time showed any evidence of a bleeding tendency. His platelet count was 270,000 per mm.^{3}, and no thrombocytopenia developed during his first week of life, the period for which he was observed (table 8).

These two cases are considered to represent examples of maternal thrombocytopenia in which platelet agglutinins have played no rôle in pathogenesis, and as a consequence, the infants' platelets were normal.

On the basis of the few cases of thrombocytopenia in pregnancy and the newborn which have been studied, it would not be reasonable to imply that other mechanisms are not at times responsible and may not be of even greater importance than those postulated above. The data available at present do, however, suggest that:

1. If the mother has a sufficiently high titer of an autoagglutinin for platelets, so that the agglutinin passes the placental barrier, the baby should have purpura.
2. If she has an isoagglutinin for the baby's platelets, presumably developed in a manner similar to Rh isoimmunization and probably an incomplete antibody, the baby should have purpura.
3. The mother may have extensive purpura, but if it is not due to a circulating platelet agglutinin the baby should be normal.

Comment

The divergence of opinions about the pathogenesis of idiopathic thrombocytopenic purpura has already been discussed. Evidence summarized in this presentation suggests that the disease may not be a specific entity, but a syndrome which may develop as a consequence of more than one abnormal mechanism.[89, 9, 90, 91] It seems reasonable to believe that ultimately one may be able to attribute the disorder in some instances to a deficiency of a factor or factors necessary for platelet formation; in others, to suppression of platelet production by metabolic or splenic dysfunctions; and in others, to excessively rapid platelet destruction. Before such differentiation can become possible, better methods for studying rates of platelet formation and destruction must be devised.

A beginning, however, can be made. The thrombocytopenic factor which has been demonstrated in the plasma of many patients with idiopathic thrombocytopenic purpura probably causes accelerated breakdown of platelets. The evidence for this is two-fold: (a) the rapidity with which plasma containing the factor causes thrombocytopenia when it is transfused into normal recipients, and (b) the fast rate at which transfused platelets dis-

appear from the circulation of patients known to have the factor. The thrombocytopenic substance may be a platelet antibody, since its presence seems to be associated with a platelet agglutinin. It is therefore presumably an immune body which might be expected to alter megakaryocytes as well as platelets, and thereby cause a decrease in platelet formation. Observations on the bone marrow of normal recipients who have been given plasma containing the factor tend to support that conclusion.[15, 16, 26] It is therefore suggested that the thrombocytopenia which occurs in association with the thrombocytopenic factor is caused both by abnormal destruction and by deficient production of platelets. On the other hand, in those patients with thrombocytopenia who develop their disease in the absence of a platelet antibody, there seemed to be only inadequate formation of platelets. Their plasma does not cause a lowering of the platelet count in normal recipients, and platelets transfused into them seem to survive normally.

The possibility that an increased potential for platelet production is induced in normal recipients of plasma from patients with idiopathic thrombocytopenia is suggested by the observation that supernormal platelet levels commonly followed the thrombocytopenic phase in the recipients. The nature of the vascular abnormality in idiopathic thrombocytopenic purpura needs further clarification. There is general agreement that capillary function is altered,[42, 77, 78, 92, 93, 94] but its relationship to the low platelet level has not been precisely defined.

Although the management of idiopathic thrombocytopenia has been facilitated by the use of adrenal cortical hormones,[95, 77, 96, 78, 79, 97, 98, 99, 100, 101, 102] many patients fail to respond either to this therapy or to splenectomy.[103, 104, 105] The suggestion is made that in some patients therapeutic failures from splenectomy result when a high concentration of platelet agglutinins persists after the operation so that rapid destruction continues in the absence of the spleen, and megakaryocytes continue to be affected by the antibody. In addition, it appears likely that the spleen is of less importance in the pathogenesis of the disease when platelet antibodies are not demonstrable. Methods for physiologically correcting the low platelet count are limited because of deficiencies in current knowledge concerning the processes which regulate normal formation, delivery and destruction of platelets. Furthermore, there is little likelihood that platelet transfusions [23, 106, 26, 107] will prove to be of value in the long-term management of most cases of idiopathic thrombocytopenia, even after platelet typing and cross-matching technics are more fully developed.

Summary

Evidence has been presented to indicate that an immunologic mechanism is responsible for the low platelet count in many cases of idiopathic thrombocytopenic purpura:

1. Platelet agglutinins have been demonstrated in vitro in the plasma of many patients whose thrombocytopenia was of the idiopathic variety.
2. A factor presumably identical to this platelet agglutinin is capable of inducing thrombocytopenic purpura and altering megakaryocytes in normal recipients of this plasma.

Remission following splenectomy is not necessarily accompanied by disappearance of the thrombocytopenic factor from the patient's plasma, a correlation which is seen in spontaneous remissions and those induced by ACTH or cortisone.

The spleen probably serves at least two functions in the pathogenesis of idiopathic thrombocytopenic purpura: that of removal of sensitized platelets, and that of producing some of the platelet agglutinin.

The lack of evidence for increased platelet destruction in some patients indicates that idiopathic thrombocytopenic purpura probably is a syndrome which may also arise solely from failure of megakaryocytes to produce circulating platelets.

Reference was made to the existence of serologically different platelet types.

Neonatal thrombocytopenia may develop as a result of transmission across the placenta of maternal autoagglutinins for platelets, or it may be due to development of isoagglutinins because of fetal and maternal platelet incompatibilities.

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OBSERVATIONS ON THE RELATIONSHIP OF PAIN TO THE PROCESS OF MYOCARDIAL INFARCTION, AS SHOWN BY ELECTROCARDIOGRAPHS IN "LATENT" CASES *

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THE cause of the pain in angina pectoris and in myocardial infarction has been considered by most observers to be myocardial ischemia and consequent abnormal metabolism due to lack of oxygen or accumulated metabolites.[1, 2] Some have postulated distention of vessels proximal to the obstruction as a cause of pain,[3] and others, distention of the infarcted area of myocardium with each heart beat.[4] The cases herein described support the concept of ischemia and its consequences as the cause of pain. They also give electrocardiographic support to and explanation of the syndrome of premonitory pain in coronary thrombosis described by Feil.[5] The term "latent" myocardial infarction would seem appropriate to these cases, and perhaps to those described by Freedberg et al. as "coronary failure" [6] and by Master as "acute coronary insufficiency." [7]

Each of these five cases developed a myocardial infarction while under observation for pain similar to that described by Feil [5] (a continuous, burning, oppressive pain, not dependent on effort or exertion, lasting one or two days or more). In our cases, prior to the episode of infarction and coincident with the period of pain, the electrocardiograms showed in each case an "ischemic" pattern of the type described by Bayley and LaDue,[8] Hecht [9] and others. With the cessation of pain the electrocardiograms showed in each case the diagnostic electrocardiographic pattern of infarction. This disappearance of pain coincident with the appearance of an infarction pattern in the electrocardiogram suggests that the infarcted area itself does not produce pain, and also that distention of vessels proximal to the occlusion is not the cause of pain. The pain, coinciding with the ischemic pattern and disappearing with the infarction pattern, would seem to be ischemic in origin. The ischemic area coincided generally with the area subsequently involved in the infarction. The series gives a clinical counterpart to the Bayley and LaDue experiment.

CASE REPORTS

Case 1. A 66 year old retired rancher developed pain in the upper anterior chest while putting out a grass fire on June 8, 1951. The pain did not radiate; it improved

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with rest. Studies including an electrocardiogram (not available) were reported as normal. A similar but less severe pain recurred three days later and an electrocardiogram barely suggested a subendocardial ischemia (figure 1, 6–19–51, V_5). Similar symptoms of moderate severity recurred during the following three weeks. In July, after a vigorous walk, he developed severe epigastric pain with vaguely described radiation into the chest and down the left arm, accompanied by severe nausea. The electrocardiogram on this occasion showed less of the ST depression than previously. (Electrocardiogram not shown.) His symptoms recurred intermittently, both on exertion and at rest. He became increasingly truculent with all who attempted to care for him, and eventually quarreled with his physician over alleged neglect. He was re-admitted in August still complaining bitterly of vaguely described thoracic and epigastric pain, nausea and belching. Although his electrocardiogram had now changed to what might be interpreted as an ischemic pattern, the finding of

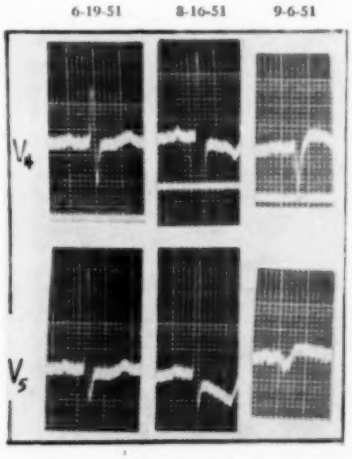

FIG. 1. *Case 1.* The record of 6–19–51 was taken during an investigation for pain but not while pain was present. It was interpreted as "possibly ischemic" because of the depressed ST with preservation of T in V_5. The record of 8–16–51 was taken preoperatively and was interpreted as "ischemic," but its clinical importance was discounted. The striking change to an infarction pattern which occurred coincident with the terminal episode of cardiovascular collapse and disappearance of pain is shown by comparing V_4 and V_5 in the records of 8–16–51 and 9–6–51.

gall-stones, plus his belligerent demand that he be given relief, led to a cholecystectomy which was performed without incident during surgery. From the third to the fifth postoperative day he complained of distress in the chest, which was discounted as due to the recent operation and postoperative bindings.

One week after leaving the hospital he suddenly collapsed and was re-admitted with extreme dyspnea, cyanosis and sweating but, for the first time during the entire illness, totally free of pain. The electrocardiogram showed an anterior myocardial infarction in the area previously shown as ischemic (figure 1, 9–6–51, V_4 and V_5). He developed progressive heart failure and pulmonary edema and died five days after admission despite vigorous measures.

An autopsy confirmed the location of the infarction and placed the duration as about seven to 14 days. This would coincide with either the subsidence of pain postoperatively or his final reëntry into the hospital.

Comment: This man, like those whose histories follow, desperately sought relief from pain which, in his case, always suggested but was seldom clearly myocardial in origin. The period of his extreme pain and distress was associated with only normal or ischemic patterns in the electrocardiogram. The development of a myocardial infarction in the area previously ischemic was associated with relief from pain.

He was a truculent, demanding, dissatisfied patient during the three month period of his pain. The pain was described with difficulty, although he was very articulate in his irascibility. The pain occurred both on exertion and at rest, yet at times exertion was well tolerated; in fact, the development of pain at rest when he was following his doctor's advice seemed to contribute to his dissatisfaction.

Case 2. This hyperkinetic, 45 year old physician had his first pain in the fall of 1949 while operating. It was between the shoulder blades and required codeine for relief. The pain recurred intermittently through 1950, both on exertion and while at rest in bed. It changed somewhat to center in the epigastrium and was increasingly

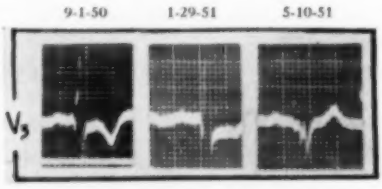

FIG. 2. *Case 2.* The first two records of 9–1–50 and 1–29–51 were taken during consultation to investigate pain, the latter record following by one day an exercise test during which an auricular tachycardia developed. The depressed ST segments in V_5 are especially noteworthy. Shortly after the record of 1–29–51 the patient entered a phase of extreme fatigue but no pain. It was during this period of freedom from pain that the record of 5–10–51 was taken, showing a slurred Q with elevated ST in V_5, the site of the previous tall R and depressed ST.

associated with gas and bloating, together with some radiation into the left arm and head. An electrocardiogram taken by us in consultation on September 1, 1950, showed inverted T in V_4 through V_6 and was reported as ischemic. Although symptoms continued, subsequent records taken elsewhere were normal.

In January, 1951, he returned to us deeply concerned about his pain and wishing further confirmation of his diagnosis, which he felt was angina. He feared that his local physician, a close personal friend, knew his immoderate habits too well to be thoroughly convinced of the reality of his trouble. For further confirmatory evidence toward the diagnosis, an exercise electrocardiogram was cautiously done, but a temporary auricular tachycardia ensued. A record the next day, however, showed again an ischemic pattern in the anterior chest leads.

Shortly thereafter his pain disappeared and was replaced by marked fatigue. Another electrocardiogram showed the development of a definite infarction in the area of previous ischemia (figure 2, 5–10–51, V_5). He was free of pain but not fatigue for about four months before he again developed anginal pain, which persists.

Comment: This hard driving, high living physician suffered baffling pain for about 16 months, during which time his electrocardiogram only occa-

sionally showed ischemic abnormalities. His pain drove him repeatedly to seek the advice of other physicians in addition to his own. Subsidence of pain coincided with infarction of the previously ischemic area, as shown by the electrocardiogram.

Case 3. A 55 year old garage owner * had had pains in the chest for several years with increasing frequency and severity. They had occurred both with and without exertion and lasted minutes to hours.

Two weeks prior to admission he suffered his most severe attack while fishing quietly from a boat. Pain radiated to both arms, and extreme bloating and belching accompanied the pain. Both the bloating and the pain waxed and waned but never subsided, despite earnest measures by his local physician.

When first seen by us he complained of epigastric and substernal pain, with extreme bloating. The distention was so extreme that, despite the impression of myo-

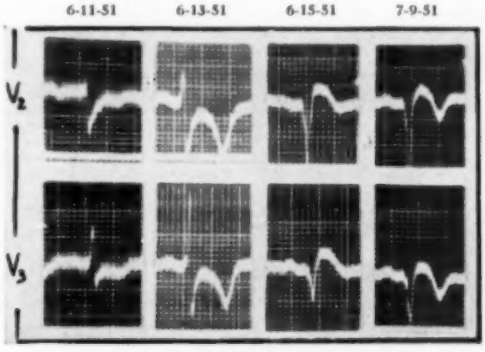

FIG. 3. *Case 3.* The first record of 6–11–51 coincided with marked gas and considerable chest pain and was interpreted as "ischemic" because of the ST depression as in V_4 with relative preservation of T. As chest distress became unbearable, producing an acute mania, the record of 6–13–51 was inscribed, showing further changes of ischemia, especially in V_2 and V_5. The record of 6–15–51 was taken only a few hours after the abrupt cessation of intractable pain and mania. It clearly demonstrates in the same leads as previously ischemic, V_2 and V_5, the appearance of a classic infarction pattern, with deep slurred Q and elevated ST.

cardial infarction, nasogastric suction was instituted with relief of gas but not of pain. The pain, in fact, increased steadily in intensity despite oxygen, Demerol in large amounts, and sedation. The patient, writhing in pain, became vituperative and maniacal toward all who came near. During the last 48 hours of pain he received 1,300 mg. of Demerol, 1.6 gm. of phenobarbital and 0.2 gm. of codeine, plus other adjuvants. Nothing relieved pain and agitation for more than one or two hours. During this stormy period of trial to all concerned, electrocardiograms taken on June 11 and June 13, 1951, showed only an ischemic pattern.

On the fourth hospital day pain suddenly subsided and the maniacal agitation disappeared. He required no further medication for pain throughout the subsequent three and one-half weeks of hospitalization. An electrocardiogram taken within a few hours of the cessation of pain and associated relaxation of the patient showed the development of a definite myocardial infarction at the location of previous ischemia (figure 3, 6–15–51, V_2 and V_5). He had no further pain throughout a long hospital and home convalescence.

* Seen through the courtesy of Dr. John W. Schubert, of Lewistown, Montana.

The patient died about three months later, under the observation of his local physician, with a sudden recurrence of severe pain and total collapse. Neither electrocardiogram nor autopsy was obtained.

Comment: This case showed only an ischemic pattern throughout the period of progressively increasing pain and distress of a type and severity usually associated with myocardial infarction. Yet only with subsidence of his severe pain was the ischemic pattern replaced with that of infarction in the electrocardiogram.

This patient, to a similar but even greater degree than the others, showed a persistent pain which tormented him to the point of mania.

Case 4. This obese, mildly diabetic (15 U. NPH daily), 68 year old woman began having "spells" about four to six months before being seen by us on December 6, 1951. These spells began as a "burning" in the epigastrium associated with gas,

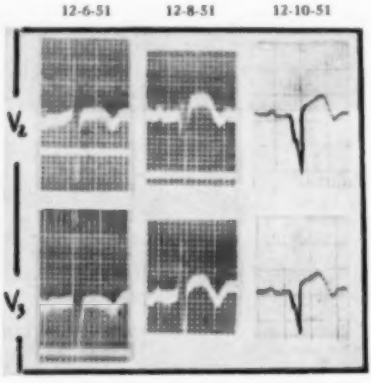

FIG. 4. *Case 4.* The original record of 12-6-51 was taken during investigation for an atypical chest distress, the T waves in V_2 and V_5 being striking clinical counterparts to those described by Bayley and LaDue in their dog experiments. Symptoms subsided greatly a few hours prior to the record of 12-8-51, which shows an infarction pattern in V_2. This is seen to be more extensive two days later, during which interval patient continued to feel strikingly better.

plus radiation to the chest below the sternum, back, left arm to the elbow and the left thigh. The episodes were most likely to occur about 11 p.m., without exertion, and to last from minutes to three to four hours. They often followed a strenuous day. She had seen several different doctors and had been hospitalized for 10 days without benefit. Four months prior to being seen, she had had a "stroke" which left no residual. She had had a "thrombosis" eight years previously, following which she had taken some digitalis preparation very irregularly.

Her spells continued on bed-rest the first four days in the hospital and required nitroglycerin frequently for relief. Blood sugar coincident with pain was 117 mg. per 100 c.c. Her electrocardiogram on the second hospital day showed only an "ischemia" pattern. During the night of the fourth hospital day she remarked that the oppression in her chest had suddenly ceased and that she felt "better than I have in months." An electrocardiogram taken the next morning showed an unequivocal

infarction pattern in the area of previous ischemia (figure 4, 12–8–51, V_3). Her "spells" did not recur during three weeks of subsequent hospitalization, whereas they had occurred at least once daily prior to the sudden change.

Comment: In this case, prolonged pain of anginal-type was present for months, yet the electrocardiogram showed only "ischemia." The pains were severe enough for her to consult several physicians, none of whom could give relief or a diagnosis. The spells ceased abruptly during the 72 hour interval in which the electrocardiographic pattern changed from ischemia to that of a classic myocardial infarction. The infarct occurred in the ischemic area. The pain and oppression ceased with the infarction.

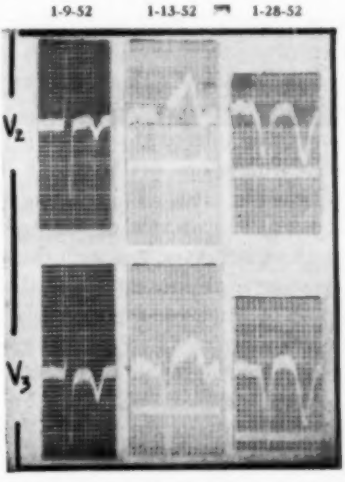

FIG. 5. *Case 5.* The first tracing (1–9–52) showed a striking duplication of the pattern described in early reversible ischemia by Bayley and LaDue. This is shown in V_2 and V_3 with a sharp symmetrical inversion of T. This pattern coincided with rapidly developing angina decubitus. Just after relief from a final extreme pain these patterns were replaced on 1–13–52 with infarction patterns in V_2 and V_3— deep slurred Q and elevated ST. Intermittent increasing daily distress disappeared after the infarction pattern occurred.

Case 5. A 65 year old retired rancher developed pain in the chest on exertion about three weeks prior to being admitted to the hospital. The pain originally came on with exertion and was relieved by rest or nitroglycerin. During the week prior to admission, however, it intensified to the point where it came on even during bed-rest. An electrocardiogram during this period showed only an ischemic pattern (figure 5, 1–9–52, V_2 through V_6).

The pain reached a climax in an episode coming after a light lunch in bed, the excruciating pain lasting two hours until relieved by morphine hypodermically. He was immediately hospitalized, where an electrocardiogram now showed a myocardial infarction in the site previously ischemic (figure 5, 1–13–52, V_2, V_3). Following the one injection of morphine, and coincident with the demonstration of the infarction, no further pain occurred. His electrocardiogram has undergone the expected evolution. He has made an uneventful recovery.

Comment: This man suffered rapidly developing angina decubitus but showed only ischemia in the electrocardiogram. With the development of an infarction at the site of the previous ischemia, anginal pain ceased and has not recurred.

Discussion

These cases all had pain for prolonged periods. The pain was anginal in type and was associated with ischemic patterns in the electrocardiogram. The pain in each case ceased abruptly and this was coincident with the development of an infarction pattern in the electrocardiogram at the site of the previous ischemia. These cases apparently went through a prolonged but progressive period of myocardial "distress," culminating in an infarction. The slow-motion pattern of the clinical course gives an opportunity to see in man the counterpart of the Bayley-LaDue experiment. It seems to show that the pain coincides with the ischemic phase and not with the infarction.

From these cases one could infer that the pain usually associated with an acute myocardial infarction develops not from the infarcted area itself but from the surrounding ischemic area. Pain, then, would roughly correlate with the suffering but not yet dead area of the myocardium. Pain would correlate with the amount of ischemia, not with the amount of dead muscle. If these deductions are proper, all measures aimed at maintaining viability of the heart muscle should be employed vigorously during the period of pain and ischemia, and prior to the time of infarction, especially if the warnings of pain and ischemic electrocardiographic pattern are given.

These cases seem to form a clinical entity which might be termed "latent" myocardial infarction. In each case the patient experienced a pain which followed the pattern described by Freedberg et al. and by Feil: persistent but infrequent pain, poorly responsive to nitroglycerin, coming on both with and without exertion, and (in our cases and in Feil's) going to infarction. The electrocardiographic pattern, when obtained, is that described by Bayley and LaDue, and by Hecht and others. The cases described here went on to infarction, but we have had others with similar patterns who have not yet done so. The term "latent," therefore, seems appropriate. The term has an implication of reversibility, which is desirable if we are correct in deducing that we are describing dying but not yet dead muscle.

These cases are similar in yet another way: each became profoundly upset by the persistent recurrent pain which he felt was due to his heart but which his original physician could not definitely label as such. Each became bitterly dissatisfied with measures taken for his aid. Each was suspected of being psychoneurotic until the electrocardiographic pattern was obtained and identified. Eventual infarction of the myocardium was in each case the only development which gave relief.

Summary

1. Five cases are described in which pain coincided with an ischemic pattern in the electrocardiogram; disappearance of pain coincided with the development of an infarction pattern in the electrocardiogram.

2. These cases are presented as evidence that ischemia and not the infarcted area is the cause of coronary pain.

3. It is inferred that pain would be a rough index not of degree of infarction but of degree of ischemia.

4. These cases are thought to be examples of recognizable "latent" myocardial infarction. They probably fall within the groups termed "coronary failure" or "acute myocardial insufficiency."

Additional Note

A sixth case observed by us falls within this group except that the area of ischemia (which was localized only once in the electrocardiogram during the course of four months of increasing anginal pain) was not in the area eventually involved by the infarction. We presume this to mean that the area of ischemia was widespread and variable, waxing and waning in at least two sites. One site went on to recovery, the other went on to infarction.

This case is of further interest because of the development of an extremely severe bilateral shoulder hand syndrome,[10] two months *prior* to the eventual infarction and two months *after* the original development of anginal symptoms. This will be reported separately.

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CARDIAC CATHETERIZATION IN THE DIAGNOSIS OF ADULT HEART DISEASE*

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INTRODUCTION

THE technic of cardiac catheterization was introduced in this country by Cournand and Ranges.[2] This procedure has resulted in considerable increase in our knowledge of pulmonary circulatory dynamics and of congenital and acquired heart disease. The method is as follows:

In the basal adult, a median antecubital vein is exposed under procaine local anesthesia, and a number seven, eight or nine nylon and plastic catheter, 100 cm. or 125 cm. in length, is inserted. The lumen of the catheter is kept patent by means of a slow drip of 5 per cent dextrose in water, containing 20 mg. of heparin per liter. Under fluoroscopic visualization, and with constant electrocardiographic observation, the catheter is advanced into the right atrium, the right ventricle and the pulmonary artery. Then an indwelling arterial needle is inserted into the brachial or femoral artery. Cournand [12] has stressed the desirability of attainment of a "steady" state before the measurement of pressures or the collection of blood and expired air samples. This state is characterized by relative constancy of respiration, pulse rate, respiratory quotient, oxygen consumption and emotional stability.

After the "steady" state is attained, measurement of pressures and the collection of blood samples may begin. Pressures may be measured satisfactorily by means of strain gauges, electromanometers or optical manometers. Saline manometers may be used for mean pressures. The zero level for pressure measurements is taken at 10 cm. upward from the back of the horizontal subject. Pressures are measured over two or more respiratory cycles.

Normal pressure in the right atrium varies from zero to 5 mm. of mercury. It is increased in failure of the right ventricle and in constrictive pericarditis. The pressure curve is characteristically deformed in constrictive pericarditis. The curve in the right atrium may also be of aid in the diagnosis of tricuspid insufficiency. During diastole, right atrial pressure is usually equal to that in the right ventricle. Normal right ventricular pressure ranges from 18 to 30 mm. mercury in systole, and from zero to 5 mm. mercury in diastole. The diastolic pressure is elevated in failure of the right ventricle and in constrictive pericarditis. The systolic pressure is elevated whenever the pulmonary artery systolic pressure is elevated and,

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in addition, in pulmonary valvular stenosis. In the latter condition, cardiac catheterization is of great diagnostic importance. Pulmonic stenosis may be assumed to be present when there is a definite pressure increase from a low or normal pulmonary artery pressure to an elevated right ventricular systolic pressure. Normal pulmonary artery pressures are 18 to 30 mm. mercury in systole, and 6 to 12 mm. mercury in diastole. These pressures may be elevated in the presence of left ventricular failure, in mitral stenosis (but not necessarily in the early stages), in chronic lung disease, in Eisenmenger's syndrome and in primary pulmonary hypertension. Pulmonary "capillary" pressures, obtained as described below, are normally from 6 to 12 mm. mercury, and are presumed to reflect left atrial pressure. The normal pulmonary "capillary" pressure pulse has two positive waves for each cardiac cycle. The first of these is due to atrial systole; the second is probably associated in some way with ventricular contraction. The second wave may become abnormally prominent in the presence of mitral incompetency. The pulmonary "capillary" pressure is elevated in the presence of symptomatic mitral stenosis and in left ventricular failure. It is normal in cor pulmonale, and may be of diagnostic aid for this reason. Occasionally the catheter enters the left atrium through a septal defect. The pressure here is normally from 4 to 8 mm. of mercury. The catheter may enter the aorta either through a ventricular septal defect or if the aorta overrides the right ventricle. In the latter instance, systolic pressures in the aorta and right ventricle tend to be identical.

Blood samples for analysis are collected in quantities of 10 c.c. in oiled heparinized syringes, and are stored in ice water over mercury. Samples are analyzed for oxygen and carbon dioxide content in the Van Slyke manometric apparatus without delay. When blood flow or cardiac output is to be measured, blood from the right heart and a systemic artery is collected simultaneously with the collection of expired air. Expired air is collected over a two minute period in a Douglas bag or Tissot tank. It is analyzed for carbon dioxide and oxygen in the Haldane or Scholander apparatus.

Since the right atrium receives blood from three major sources, i.e., inferior vena cava, superior vena cava and coronary sinus, complete mixing may not take place until the upper right ventricle or proximal pulmonary artery is reached. Inferior caval blood may be 2 vol. per cent higher in oxygen content than superior caval blood; in addition, blood from the coronary sinus is very low in oxygen content, being usually below 7 vol. per cent. Therefore, it is desirable to obtain mixed venous samples for the cardiac output from the proximal pulmonary artery unless there is a left-to-right shunt, when the right atrium or venae cavae are used.

The oxygen content of right atrial blood may vary as much as 2 vol. per cent from the average of that in the superior and inferior venae cavae. An increase in the oxygen content of right atrial blood above this level is most often due to an atrial septal defect with left-to-right shunt, but may be due

to an anomalous pulmonary vein draining into the right atrium, or to a ventricular septal defect associated with tricuspid insufficiency. Right ventricular blood oxygen content may normally vary as much as 1 vol. per cent from that in the right atrium. An increase beyond this value is most often due to left-to-right shunt through a ventricular septal defect, but may be due to patency of the ductus arteriosus, with accompanying pulmonary valvular insufficiency. Pulmonary artery blood oxygen content may vary as much as 0.5 vol. per cent from that in the right ventricle. An increase in pulmonary artery blood oxygen content beyond this level is usually due to patency of the ductus arteriosus, but may occur in any aortic-pulmonary communication, such as an aortic septal defect. Occasionally this finding may be associated with a high ventricular septal defect in which there is little mixing within the right ventricle. For this reason, in suspected congenital heart disease, multiple samples in the various heart chambers should be taken. Systemic arterial blood is normally 94 to 100 per cent saturated with oxygen, as is the pulmonary "capillary" sample. Significant unsaturation of the arterial blood is usually due to lung disease or right-to-left shunt; unsaturation of the pulmonary "capillary" blood is usually due to lung disease and does not occur in the presence of right-to-left shunt.

The following formulae, taken from Bing,[4] may be used to estimate cardiac output, systemic and pulmonary flow, and the volume of shunts.

$$\text{Cardiac Output (c.c./min.)} = \frac{\text{O}_2 \text{ intake (c.c./min.)}}{\text{O}_2 \text{ content arterial blood (vol. \%)} - \text{O}_2 \text{ content mixed venous blood (vol. \%)}} \times 100$$

$$\text{Pulm. Art. Flow} = \frac{\text{O}_2 \text{ intake (c.c./min.)}}{\text{Pulm. venous O}_2 \text{ content (vol. \%)} - \text{pulm. arterial blood O}_2 \text{ content (vol. \%)}} \times 100$$

Pulmonary venous blood is assumed to be saturated 95 per cent of capacity.

$$\text{Systemic flow} = \frac{\text{O}_2 \text{ intake (c.c./min.)}}{\text{Systemic arterial O}_2 \text{ content} - \text{mixed venous O}_2 \text{ content}} \times 100$$

$$\text{Effective pulmonary artery flow} = \frac{\text{O}_2 \text{ intake (c.c./min.)}}{\text{Pulm. venous O}_2 \text{ content} - \text{mixed venous O}_2 \text{ content}} \times 100$$

Total left-to-right shunt = pulmonary artery flow—effective pulmonary artery flow.

Total right-to-left shunt = systemic flow minus effective pulmonary artery flow.

Pulmonary arteriolar resistance may be estimated from a formula which is given below.

$$R = \frac{PA - PC}{CO} \times 1332$$

where R = pulmonary arteriolar resistance in dynes seconds/cm.$^{-5}$
PA = mean pulmonary artery pressure in mm. Hg
PC = mean pulmonary "capillary" pressure in mm. Hg
CO = cardiac output in c.c./sec.

This value is increased above the normal in Eisenmenger's syndrome, left ventricular failure, and in primary pulmonary hypertension. It may be increased in mitral stenosis and in chronic lung disease.

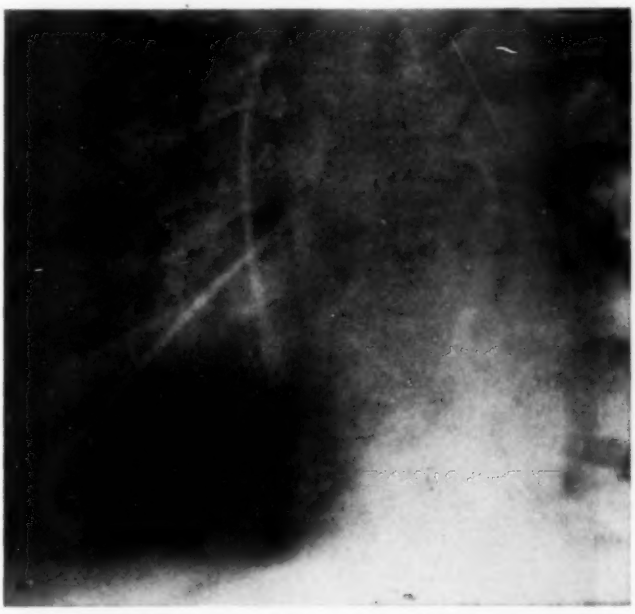

FIG. 1. The roentgenogram shows the catheter wedged into a small branch of the right pulmonary artery in position for recording pulmonary "capillary" pressure.

CLINICAL USE OF CARDIAC CATHETERIZATION

Although the chief value of catheterization of the right side of the human heart has been as a physiologic tool and as an aid in the diagnosis of congenital heart disease, the procedure may also be of help in acquired heart disease. The following paper describes 15 cases of adult heart disease of varying etiology in which cardiac catheterization was employed in diagnosis and management and found to be a practical device. The patients studied were from the medical wards of the Cincinnati General Hospital and from the medical service of the Veterans Administration Hospital, Dayton, Ohio (a Dean's Committee hospital). The cases presented were selected from 128 studied by this method during the past two years.

Contraindications

The following were considered contraindications to the performance of cardiac catheterization [1]: spontaneous premature contractions, recent history of paroxysmal arrhythmia, subacute bacterial endocarditis unless arrested for three months or more, recent myocardial infarction, myocarditis and

Fig. 2. The roentgenogram shows the catheter wedged into a small branch of the left pulmonary artery in position for recording pulmonary "capillary" pressure.

auricular fibrillation. The procedure is done, however, if indicated in mitral stenosis with auricular fibrillation from the standpoint of possible valvulotomy.

Complications

In the 128 cases the following complications were observed: Mild thrombophlebitis of the vein employed was common but was temporarily

incapacitating in only a few instances. A small pulmonary embolus occurred in one patient who recovered satisfactorily. Right bundle branch block lasting for from one to 12 hours was seen in eight patients. Auricular fibrillation lasting only a few hours occurred in one patient, and bigeminal rhythm due to ventricular premature contractions lasted for one hour in another. Premature auricular, nodal and ventricular contractions were seen in almost every patient when the catheter tip was present in the appropriate chamber.

Method

Venous catheterization of the right side of the heart and of the pulmonary artery was performed in the manner of Cournand and Ranges.[2] A vein on the medial surface of the forearm was used. The position of the catheter tip was determined by fluoroscopy and by pressure curves recorded by the Hathaway blood pressure recording apparatus. A direct writing electro-

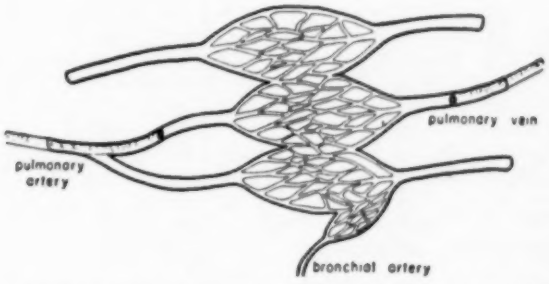

Fig. 3. A diagram of the pulmonary "capillary" circulation, showing the position of the catheter when wedged into a small branch of the pulmonary artery. (From Hellems, H. K., Haynes, F. W., Dexter, L., and Kinney, T. D.: Pulmonary "capillary" pressure in animals estimated by venous and arterial catheterization, Am. J. Physiol. **155**: 98, 1948; reproduced by permission of the publishers and author.)

cardiograph was observed closely as the catheter was advanced through the heart. Pulmonary "capillary" pressure was determined as described by Hellems and coworkers.[3] This pressure is considered to vary with the pulmonary venous pressure, and is obtained by wedging the catheter tip into a small branch of the pulmonary artery in a distal portion of the lung. Fully oxygenated blood could often be withdrawn from the wedged catheter tip. In other instances nothing could be aspirated. Figures 1 and 2 are roentgenograms showing the catheter tip in position for measurement of pulmonary "capillary" pressure. Figure 3 shows diagrammatically the position of the wedged catheter tip. Figure 4 shows redrawn and superimposed curves indicating the relation of the pulmonary "capillary" pressure pulse to right atrial and pulmonary artery pressure tracings.

Cardiac outputs were measured by the direct Fick method. Mixed venous samples were obtained from the proximal portion of the pulmonary

artery. Arterial blood samples were withdrawn simultaneously from the brachial or femoral artery. Blood samples obtained during the collection of expired air were analyzed for oxygen in the Van Slyke manometric apparatus and were required to check within 0.2 vol. per cent. Two minute samples of expired air were collected in Douglas bags, measured in a Tissot spirometer, and analyzed for carbon dioxide and oxygen in the Haldane apparatus. Duplicate samples were required to check within 0.03 per cent. Shunts were calculated by the formulae of Bing.[4] Cross sectional valve areas were determined from the formulae of Gorlin and Gorlin.[5] The fol-

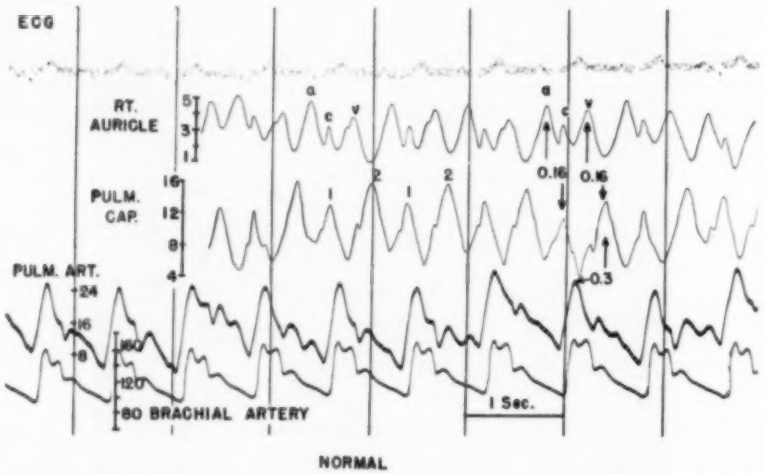

FIG. 4. The photographic record shows the relationship between the pressure pulse tracing obtained in the right atrium, pulmonary "capillary," pulmonary artery and brachial artery. Note that the pulmonary "capillary" pressure pulse consists of two positive waves, the first of which follows closely the "A" wave of the right atrial pulse, the second of which follows by the same interval the "V" wave of the right atrial pressure pulse. Note also that there is a considerable time interval between the pulmonary artery systolic peak and the second wave of the pulmonary "capillary" pressure pulse. The pressures are expressed in mm. Hg; the curves are superimposed and redrawn, using an electrocardiogram for timing.

lowing values are considered normal for the measurements made in this laboratory.

Right atrium mean pressure 0–5 mm. Hg
Right ventricle 18–30 systolic; 0–5 diastolic mm. Hg
Pulmonary artery 18–30 systolic; 6–12 diastolic mm. Hg
Pulmonary "capillary" mean pressure 6–12 mm. Hg
Cardiac index 3.1 ± 0.4 L./min.
A-V oxygen difference 4.5 ± 0.7 c.c./100 c.c.
Oxygen consumption 138 ± 14 c.c./sq. m./minute

Pulmonary arteriolar resistance 47–160 dynes seconds/cm.$^{-5}$
Mitral valve cross sectional area 4–6 sq. cm.
Arterial oxygen saturation 94–100%
SVC-RA O_2 difference = < 1.9 vol. %
RA-RV O_2 difference = < 0.9 vol. %
RV-PA O_2 difference = < 0.5 vol. %

Case Reports

Case 1. A 23 year old white man was admitted to the Holmes Hospital December 18, 1950, and discharged December 20, 1950.

History: The patient had had a heart murmur since the age of five. He had had dyspnea on exertion for several years but had not noticed cyanosis. He was referred for examination when his murmur was discovered during an Armed Service pre-induction physical examination.

Physical Examination: There was no cyanosis or clubbing. The blood pressure was 135/75 mm. of Hg. There were a systolic murmur and thrill over the precordium which were maximal in the left second intercostal space and could be detected in the neck and over the back of the thorax.

Laboratory Findings: The electrocardiogram and spatial vectorcardiogram showed right ventricular hypertrophy. Cardiac fluoroscopy showed a large main pulmonary artery whose small branches were not prominent. There was no intrinsic pulsation in the pulmonary artery. This patient's chest x-ray is reproduced in figure 5.

Impression: The clinical diagnosis was that of possible pulmonic stenosis, but because of the large pulmonary artery an atrial septal defect was considered, although the absence of intrinsic pulmonary artery pulsations militated against this.

Cardiac catheterization findings were as follows:

Pressures	*mm. Hg*	*Normal*
Pulmonary artery	18/10	(18–30/6–12)
Right ventricle	165/6.5	(18–30/0–5)
Right atrium	6.3	(0–5)
Oxygen content	*Vol. %*	
SVC	12.18	
RA	8.39	
RV	11.96	
PA	11.82	
BA	19 (96.2%)	(94–100%)
Cardiac index = 2.09 L.		(3.1 ± 0.4)
Calculated pulmonary valve area = 0.43 sq. cm.		

Comment: The marked rise in pressure as the catheter was withdrawn from the pulmonary artery to the right ventricle indicated the presence of pulmonic stenosis. The failure to find significant elevation in oxygen content as the catheter was passed from the superior vena cava into the right atrium, right ventricle and pulmonary artery militated against the presence of a left-to-right shunt. The low oxygen content of the right atrial blood sample was due to contamination with coronary sinus blood. The normal brachial arterial oxygen saturation militated against a significant degree of right-to-left shunt. The low cardiac index, slightly elevated right atrial and right

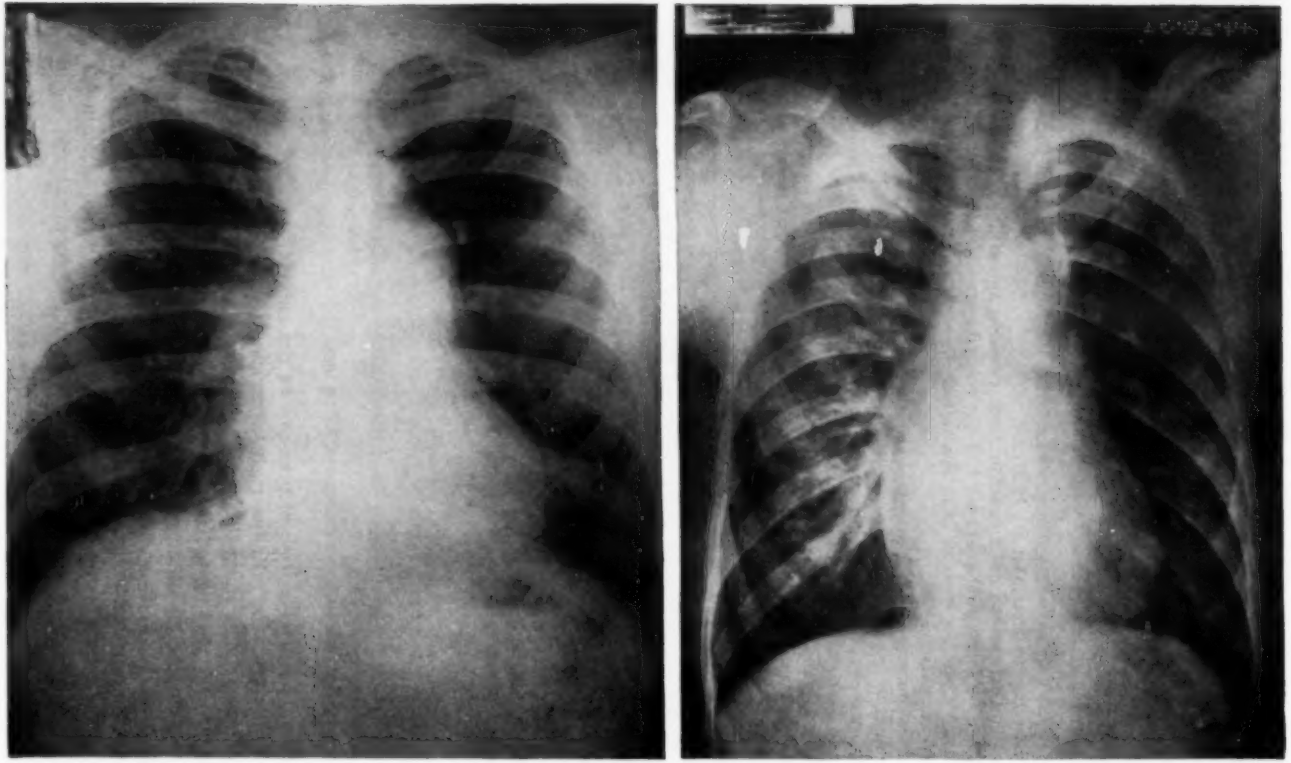

FIG. 5 (*Left*). Chest teleroentgenogram of case 1. Isolated pulmonary stenosis. The teleroentgenogram shows dilatation of the main pulmonary artery. The prominent convexity in the left superior mediastinum is the pulmonary artery, not the aortic knob. The aortic knob is superior to the pulmonary artery. In spite of the dilated pulmonary artery, the small branches of the pulmonary artery in the peripheral lung field are not enlarged.

FIG. 6 (*Right*). Chest teleroentgenogram of case 3. Patent ductus arteriosus. There is slight increase in the transverse diameter of the heart. Fluoroscopy showed active pulsations of the left ventricle and the aorta. The left atrium was slightly enlarged. There was no hilar dance.

ventricle end diastolic pressures suggest early failure of the right ventricle. The calculated pulmonary valve area was quite small, being about one tenth of the normal.

Final Impression: Isolated pulmonic stenosis. Surgical exploration was not considered warranted at the present time because of the scant experience with operation upon the pulmonic valve.

Case 2. A 20 year old colored man was admitted to Cincinnati General Hospital on September 11, 1950, and discharged September 13, 1950.

History: The patient had a history of exertional dyspnea and intermittent cyanosis since early childhood. Blood pressure was 95/80 mm. of Hg. The patient was small and poorly developed. There were clubbing and cyanosis of the fingers and toes. The heart was enlarged to the right and left. There was a precordial systolic murmur, loudest in the pulmonic area.

Laboratory Findings: The electrocardiogram showed probable "right ventricular strain." Hemoglobin was 22.4 gm. The arterial oxygen saturation was 82.6 per cent and, with exercise, fell to 48.7 per cent. There was a slight increase in oxygen consumption per liter of ventilation with exercise. Fluoroscopy was suggestive of right ventricular enlargement. There was no intrinsic pulsation in the pulmonary artery.

Impression: Probable tetralogy of Fallot, although the failure of oxygen consumption per liter of ventilation to fall with exercise was unusual.

Cardiac catheterization findings were as follows:

Pressures	*mm. Hg*	*Normal*
Mean pulmonary artery	10	(13–17)
Right ventricular	120/6	(18–30/0–5)
O_2 content	*Vol. %*	
Superior vena cava	16.82	
Right atrium	17.65	
Right ventricle	22.3	
Pulmonary artery	21.8	
Arterial O_2 saturation	85.4%	(94–100)
Systemic flow = 3.15 L./min.		(4–8 L)
Pulmonary flow = 3.54 L./min.		(4–8 L)
Left → right shunt = 1.27 L./min.		
Right → left shunt = 0.88 L./min.		

Comment: The marked rise in pressure as the catheter was withdrawn from the pulmonary artery to the right ventricle indicated pulmonic stenosis. The rise in oxygen content of the blood as the catheter was passed from the right atrium to the right ventricle indicated the presence of a ventricular septal defect. It has been shown that the patient had three of the four components of the tetralogy of Fallot, namely, pulmonic stenosis, ventricular septal defect and right ventricular hypertrophy. In spite of this diagnosis it was decided that the patient should not be operated on because of his relatively high arterial oxygen saturation and his relatively small right-to-left shunt. It was also felt that the failure of oxygen consumption per liter of ventilation to fall with exercise indicated that the pulmonary arteries were already receiving a large collateral circulation from the bronchial arteries and that the Blalock-Taussig operation would not be of benefit.

Final Impression: Tetralogy of Fallot.

Case 3. A 23 year old colored man was admitted to Cincinnati General Hospital on April 6, 1951, and discharged on May 10, 1951.

History: The patient had had a history of moderate exertional dyspnea for several years. He was known to have had a heart murmur for 11 years.

Physical Examination revealed a typical continuous murmur in the second left interspace, with systolic accentuation. The murmur was well transmitted to the left shoulder. The patient also had hypertelorism. Blood pressure was 128/84 mm. of Hg.

Laboratory Findings: The patient's x-ray is reproduced in figure 6.

Impression: Patent ductus arteriosus.

Cardiac catheterization findings were as follows:

Pressures	*mm. Hg*	*Normal*
Pulmonary artery	40/12	(18–30/6–12)
Right ventricular	46/0–6	(18–30/0–5)
O_2 Content	*Vol. %*	
Superior vena cava	15.26	
Right atrium	15.24	
Right ventricle	15.69	
Pulmonary artery	17.36	

Pulmonary flow = 11.44 L./min.
Left → right shunt = 5.18 L./min.

Comment: There was moderate elevation of pulmonary artery and right ventricular pressures which was probably partly the result of the high pulmonary flow. The rise in oxygen content of the blood as the catheter was advanced from the right ventricle to the pulmonary artery indicated the presence of a shunt from the aorta to the pulmonary artery. This is most commonly due to patent ductus arteriosus, although it could be produced by the rupture of an aneurysm of the aorta into the pulmonary artery or by an aortic septal defect. An operation was performed on April 27, 1951. A patent ductus arteriosus, 1 cm. in diameter and 3 to 4 mm. long, was ligated. At this time the continuous murmur disappeared. Postoperative convalescence was uneventful except for transient hoarseness due to left vocal cord paresis. On October 3, 1951, blood pressure was 120/80 mm. of Hg; pulse was 72. There were no cardiac murmurs.

Case 4. A 41 year old white woman was admitted to the Cincinnati General Hospital on June 4, 1951, and discharged on June 23, 1951.

History: The patient had had a heart murmur since the age of three. For two years she had had dyspnea and chest pain on exertion. Her family history was unknown.

Physical Examination revealed that the patient had a thin, gracile habitus. Her heart was enlarged. Pulmonic second sound was accentuated and reduplicated. There were a systolic murmur and thrill of maximal intensity in the fourth left intercostal space to the left of the sternum, found also at the cardiac apex. There was no cyanosis or clubbing.

Laboratory Findings: There was marked intrinsic pulsation of the pulmonary artery (hilar dance). The patient's chest x-ray is reproduced in figure 7. The electrocardiogram showed an rSR′ complex in V_1 which could have been due to either right ventricular hypertrophy or incomplete right bundle branch block. The spatial vectorcardiogram indicated right ventricular hypertrophy because of clockwise rotation of the QRS loop in the transverse plane.

Impression: The presence of large pulmonary arteries with hilar dance, right ventricular hypertrophy in the electrocardiogram, and the gracile habitus of the patient favored the diagnosis of an atrial septal defect. However, the location of the murmur was more consistent with ventricular septal defect.

Cardiac catheterization findings were as follows:

Pressures mm. Hg		*Normal*
Right atrial mean	7.4	(0–5)
Right ventricular	104/8	(18–30/0–5)
Pulmonary artery	122/38	(18–30/6–12)
Arterial O_2 saturation	93.1%	(94–100)
Superior vena cava O_2 content	11.75	
Right atrium O_2 content	15.18	
Right ventricle O_2 content	15.31	
Pulmonary artery O_2 content	15.03	
Left-to-right shunt	2.01 L./min.	

Comment: There was considerable elevation of both right ventricular and pulmonary artery pressures. The marked rise in oxygen content of the blood as the catheter was advanced from the superior vena cava into the right atrium indicated the presence of an atrial septal defect. Although such a finding could be reproduced by an anomalous pulmonary vein entering the right atrium, or by ventricular septal defect associated with tricuspid insufficiency, the clinical picture did not favor these two possibilities. The moderate elevation of right atrial and right ventricular end diastolic pressure indicated probable right ventricular failure. The patient developed clinical right ventricular failure six months following this study.

Final Impression: Atrial septal defect.

Case 5. A 27 year old white man was admitted to the Cincinnati General Hospital on December 11, 1950, and was discharged December 16, 1950.

History: The patient had had a history of cyanosis since the age of 14 and dyspnea on marked exertion since the age of 18.

Physical Examination revealed cyanosis and clubbing of the fingers. Blood pressure was 100/70 mm. of Hg. The pulmonic second sound was accentuated. There was a faint pulmonic systolic murmur.

Laboratory Findings: Hemoglobin was 21.4 gm., red blood count was 7,300,000, and hematocrit was 65. Vital capacity was 5,000 c.c. Circulation time with Decholin was 12 seconds. The electrocardiogram showed right ventricular hypertrophy. The patient's x-ray is reproduced in figure 8.

Cardiac catheterization findings were as follows:

Pressures	*mm. Hg*	*Normal*
Right ventricular	140/0–4	(18–30/0–5)
Pulmonary artery	140/80	(18–30/6–12)
Pulmonary "capillary"	8.6	(6–12)
Pulmonary arteriolar resistance	1,792 dynes seconds/cm.$^{-5}$	(47–150)
O_2 Content	*Vol. %*	
Superior vena cava	17.46	
Right atrium	18.65	
Right ventricle	20.42	
Pulmonary artery	20.78	

Systemic flow = 4,744 c.c./min.	(4–8 L)
Pulmonary artery flow = 4,165 c.c./min.	(4–8 L)
Effective pulmonary artery flow = 3,182 c.c./min.	(4–8 L)
R → L shunt = 1,562 c.c./min.	
L → R shunt = 983 c.c./min.	

Comment: The right ventricular and pulmonary artery pressures were markedly elevated. The pulmonary arteriolar resistance was over 10 times normal, indicating marked increase in tonus of the pulmonary "arterioles." The rise in oxygen content as the catheter was passed from the right atrium to the right ventricle indicated a ventricular septal defect. The combination of high pulmonary resistance and ventricular septal defect was characteristic of Eisenmenger's complex.[6] However, overriding of the aorta, which is also necessary for a definite diagnosis, was not demonstrated. Systolic pressures in the right ventricle and brachial artery should be nearly identical if recorded simultaneously; ours were not so recorded. Overriding of the aorta may also be demonstrated by passage of the catheter into the aorta from the right ventricle or by angiocardiography. The observation of higher pressure in the pulmonary artery than in the brachial artery may be seen in Eisenmenger's complex because of the very high pulmonary arteriolar resistance, which is, in this instance, greater than normal systemic resistance. Right ventricular hypertrophy was also present. The high pulmonary arteriolar resistance was responsible for the high pulmonary artery pressure and the consequent right-to-left shunt, producing cyanosis, which is not usually seen in uncomplicated ventricular septal defect.

Final Impression: Probable Eisenmenger's complex. Surgical exploration was not warranted.

Case 6. A 30 year old white man was admitted to Cincinnati General Hospital for study August 2, 1951, and was discharged August 3, 1951.

History: The patient was wounded in 1944 by a .45-caliber bullet which entered his left hip and left through his right midabdomen. Perforated intestines were repaired by laparotomy. Shortly after the operation the patient noticed a prominent pulsation in his lower abdomen. About six months prior to study he developed exertional dyspnea, dependent edema and orthopnea.

Physical Examination: Blood pressure was 150/70 mm. of Hg. The heart was enlarged to the anterior axillary line. There were an apical systolic murmur and an apical diastolic gallop. There were a loud continuous bruit and thrill over the lower midabdomen, more prominent in the right lower quadrant.

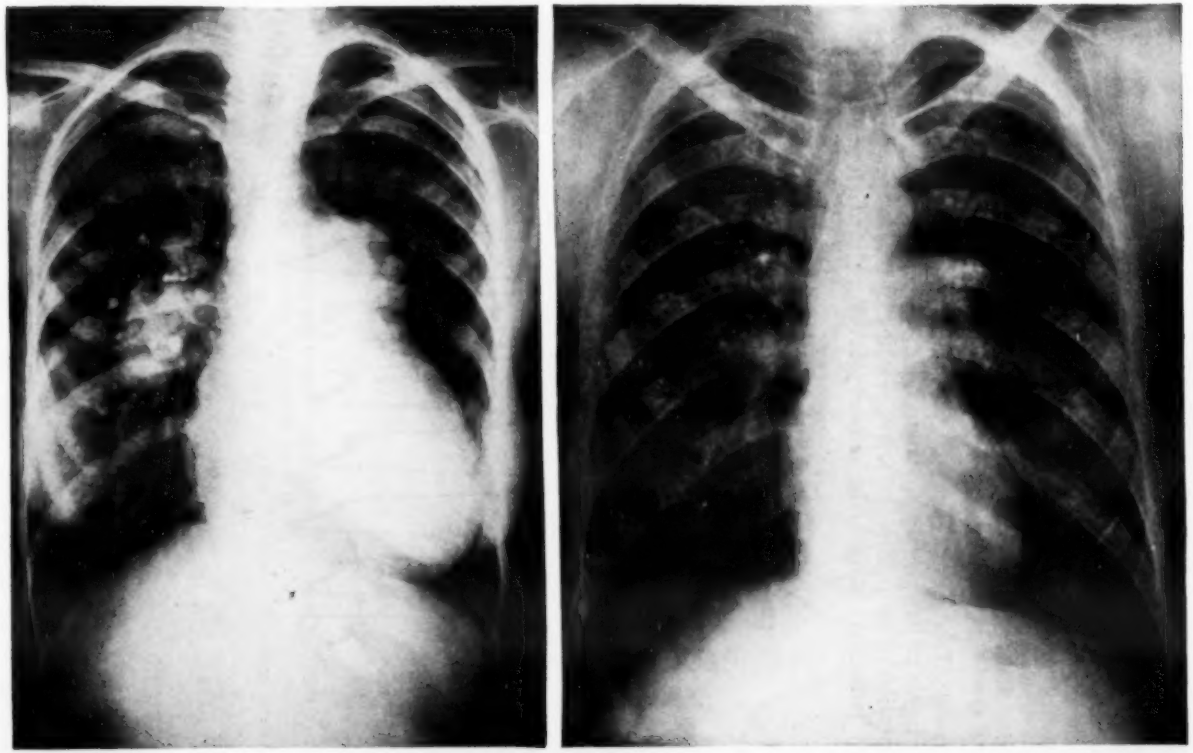

FIG. 7 (*Left*). Chest teleroentgenogram of case 4. Atrial septal defect. There is extreme enlargement of both branches of the main pulmonary artery. The right ventricle is also enlarged. Fluoroscopy showed intrinsic hilar pulsations. A small aortic knob and normal size left atrium and ventricle were also seen.

FIG. 8 (*Right*). Chest teleroentgenogram of case 5. Eisenmenger's complex. The pulmonary artery is prominent. Circulation to the lung is normal. The aortic knob is small. Fluoroscopy revealed no hilar dance and enlargement of the right ventricle.

Impression: Arteriovenous fistula between the aorta and the inferior vena cava with congestive heart failure.

Cardiac catheterization findings were as follows:

Pressures mm. Hg		*Normal*
Pulmonary "capillary"	10.96	(6–12)
Pulmonary artery mean	21.9	(13–17)
Right atrium	5.4	(0–5)
Pulmonary flow = 14.75 L./min.		(4–8)
Effective pulmonary flow = 3.76 L./min.		(4–8)
Systemic flow = 4.03 L./min.		(4–8)
L → R shunt = 11 L./min.		

Comment: The normal pulmonary "capillary" pressure indicated no marked degree of left ventricular failure at the time of study. There was slight elevation of the pulmonary artery pressure, probably the result of the increased pulmonary flow. The left-to-right shunt through the arterio-

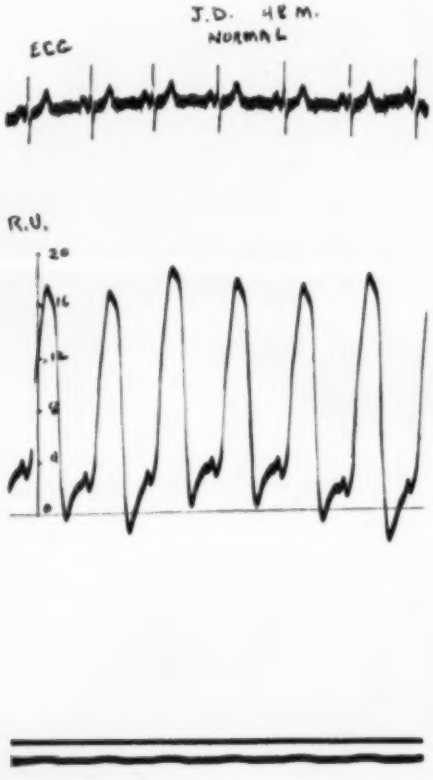

FIG. 9. Electrocardiogram and right ventricle pressure pulse curve in a normal subject. Notice that the end diastolic pressure in the right ventricle is below 5 mm. Hg.

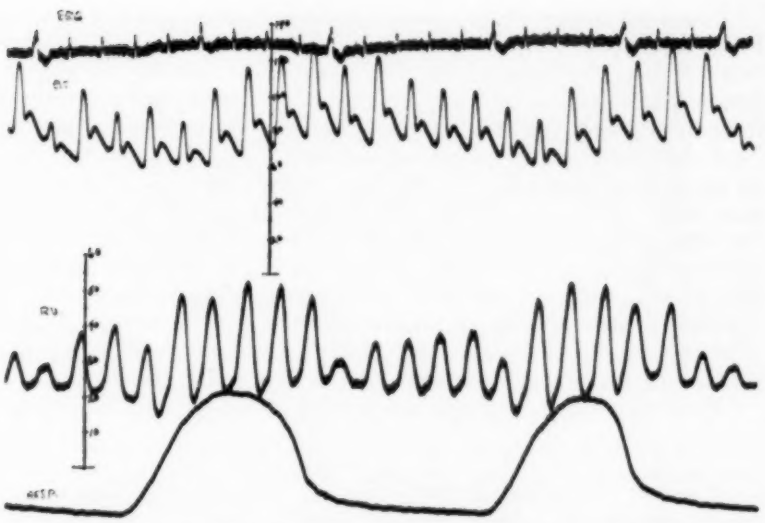

FIG. 10. Simultaneous electrocardiogram, brachial artery and right ventricle pressure pulse and respiratory tracing of case 7, with cardiac tamponade due to tuberculous pericarditis. Upward movement on respiratory curve indicates inspiration. Note marked paradoxical pulse and marked elevation in diastolic pressure within the right ventricle, producing narrow right ventricular pulse pressure.

venous fistula was 11 L. per minute. The pulmonary flow in this patient, which reflects the total cardiac output, was 14.75 L. per minute, which is more than twice normal and is characteristic of the high cardiac output seen with systemic arteriovenous fistula. Shortly after this study an arteriovenous fistula between the internal iliac artery and vein was repaired, and the heart size has returned to normal.

Final Diagnosis: Systemic arteriovenous fistula with congestive heart failure.

Case 7. A 58 year old white man was admitted to the Cincinnati General Hospital on April 1, 1950, and was discharged on May 18, 1950.

History: The patient had had chest pain for 10 days. Syncope occurred on the day of admission.

Physical Examination: Blood pressure, 100/80 mm. of Hg; temperature 100° F. The neck veins were distended. There was a paradoxical pulse. The liver was moderately enlarged.

Laboratory Findings: Venous pressure was 16 cm. of water. The electrocardiogram was compatible with pericarditis. The chest x-ray showed tuberculosis in the left apex and was also consistent with pericarditis with effusion. Sputum examination revealed acid-fast bacilli. Pericardial tap yielded a small amount of sanguineous fluid.

Impression: Tuberculous pericarditis.

Cardiac Catheterization: The intracardiac pressure curve is reproduced in figure 10.

Comment: Figure 9 shows a normal right ventricular pressure curve. For comparison, note that the right ventricular end diastolic pressure is below 5 mm. of mercury. The right ventricular systolic pressure is approximately 18 mm. of mercury. Figure 10 shows the pulse pressure record from this patient, with simultaneous recording of the brachial artery and right ventricular pressure, and respiration. The brachial artery pressure curves show a marked paradoxical pulse, as does the right ventricular pressure curve. Note the very narrow pulse pressure in the right ventricle and the extreme elevation of the right ventricular end diastolic pressure to approximately 20 mm. of mercury, whereas the right ventricular systolic pressure is only moderately elevated. This narrow pulse pressure in the right ventricle is characteristic of pericardial effusion with cardiac tamponade. The diastolic dip in the right ventricular pressure curve described in constrictive pericarditis is not usually seen in pericardial effusion.[7]

Final Impression: Tuberculous pericarditis with cardiac tamponade.

Case 8. A 53 year old colored man was admitted to the Cincinnati General Hospital on March 26, 1951, and was discharged on April 23, 1951.

History: The patient had had exertional dyspnea for seven years. One week prior to admission he developed dependent edema.

Physical Examination: Blood pressure, 100/70 mm. of Hg. Neck veins were distended.

The lungs were emphysematous and revealed wheezes. There was no cardiac murmur. There was 2 plus peripheral edema. There was slight cyanosis.

Laboratory Findings: The electrocardiogram showed right ventricular hypertrophy. The chest x-ray, reproduced in figure 11, shows cor pulmonale and emphysema.

Impression: Hypertrophic emphysema of the lungs with cor pulmonale and congestive heart failure.

Cardiac catheterization findings were as follows:

		Normal
Arterial O_2 saturation	78.1%	(94–100)
Pulmonary "capillary" O_2 saturation	84.8%	(94–100)
Arterial CO_2 content	60.8 vol. %	(45–55)
Cardiac index	3.21 L./min.	(3.1 ± 0.4)
Pressures mm. Hg		
Pulmonary "capillary"	11.6	(6–12)
Pulmonary artery	55/20	(18–30/6–12)
Pulmonary mean	35.4	(13–17)
Right atrium	4.2	(0–5)
Pulmonary arteriolar resistance	348.4 dynes seconds/cm.$^{-5}$	(47–150)

Comment: The low resting arterial oxygen saturation and the elevated arterial CO_2 content are commonly seen in severe emphysema. The low pulmonary "capillary" oxygen saturation is also seen in emphysema. The normal cardiac index in the presence of congestive heart failure is seen more commonly in emphysema than in hypertensive or valvular heart disease with failure.[8] Normal pulmonary "capillary" pressure indicated the absence of left ventricular failure and would tend to exclude such conditions as mitral

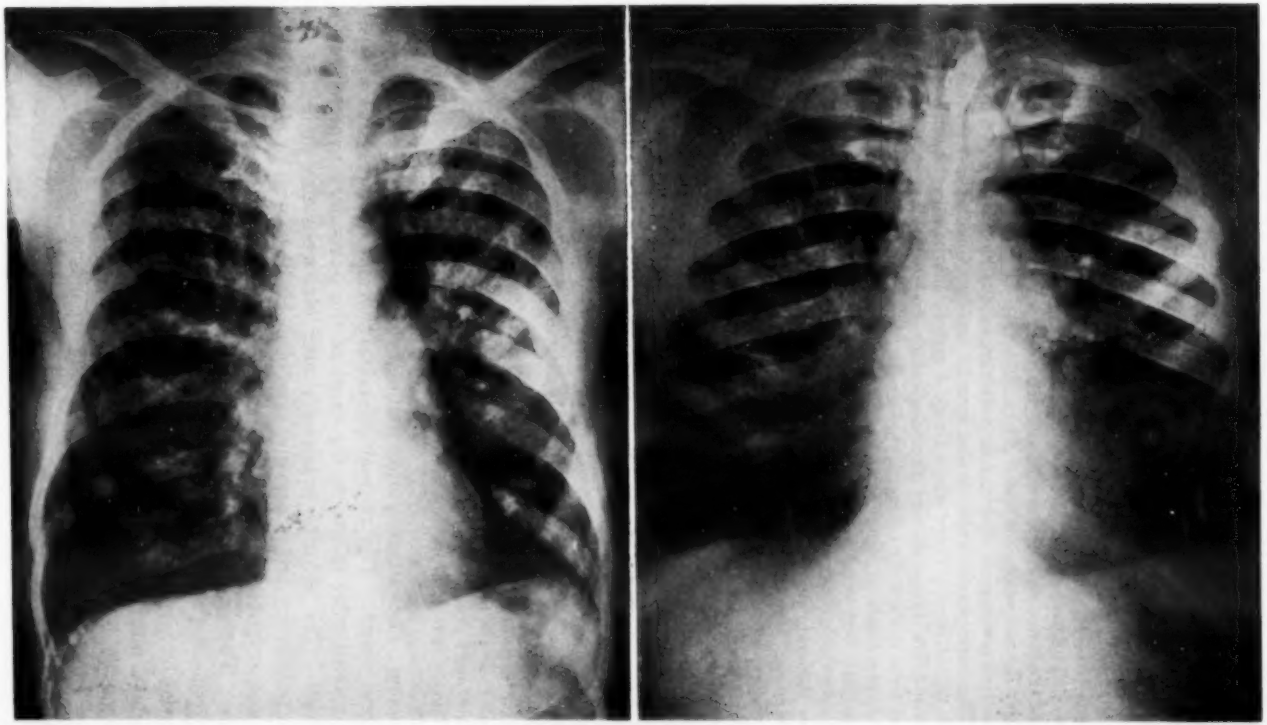

FIG. 11 (*Left*). Chest teleroentgenogram of case 8. Cor pulmonale. There is pulmonary emphysema with flattening of the right diaphragm, prominent pulmonary artery, and bilateral reticular pulmonary infiltrate. The findings are indicative of cor pulmonale.

FIG. 12 (*Right*). Chest teleroentgenogram of case 9. Cor pulmonale. The transverse diameter of the heart is normal. Pulmonary artery is full. There are emphysema in the bases and a suggestion of fine nodular infiltrate in the lung fields.

stenosis or hypertensive or arteriosclerotic heart disease with failure producing the elevation in pulmonary artery pressure. The elevated pulmonary arteriolar resistance is characteristic of pulmonary emphysema. The normal right atrial pressure indicated the absence of right heart failure at this time.

Final Impression: Pulmonary emphysema with cor pulmonale.

Case 9. A 43 year old colored man was admitted to the Cincinnati General Hospital on February 18, 1951, and was discharged on March 7, 1951.

History: The patient had had asthmatic breathing for nine years. For five years he had had exertional dyspnea, cough and dependent edema. The patient had worked in a foundry for one year.

Physical Examination: Pulse, 120; respirations 48; blood pressure, 152/90 mm. of Hg. The heart was enlarged to the anterior axillary line. The pulmonic second sound was accentuated. There was a Grade 2 systolic murmur in the third left intercostal space. The lungs showed dry inspiratory and expiratory râles. The liver and spleen were moderately enlarged.

Laboratory Findings: Red blood count was 7,400,000. Vital capacity was 42 per cent of normal, and venous pressure was 8 cm. of water. The electrocardiogram showed questionable "right ventricular strain." The x-ray is reproduced in figure 12 and shows moderate emphysema and suggested silicosis.

Impression: Hypertensive cardiovascular disease with failure and bronchial asthma. Later, when attention was called to the possible "right ventricular strain" on the electrocardiogram, the loud pulmonic second sound and the systolic murmur in the pulmonic area, the possibility of an atrial septal defect was considered.

Cardiac catheterization findings were as follows (no increase in O_2 content of blood as the catheter was passed from superior vena cava to right atrium to right ventricle to pulmonary artery):

		Normal
Arterial O_2 saturation	94%	(94–100)
Cardiac index	2.17 L./min.	(3.1 ± 0.4)
Pressures mm. Hg		
Right atrium	7.2	(0–5)
Pulmonary artery	29.0	(13–17)
Pulmonary "capillary"	10.7	(6–12)
Pulmonary arteriolar resistance	351 dynes seconds/cm.$^{-5}$	(47–150)

Comment: The catheterization findings ruled out atrial septal defect with left-to-right shunt. The normal pulmonary "capillary" pressure did not favor left ventricular failure as the cause of the pulmonary hypertension in this patient. The elevated pulmonary arteriolar resistance indicated that the high pulmonary artery pressure was probably the result of chronic lung disease and emphysema, and thus made cor pulmonale the most probable diagnosis. The cardiac index in the presence of cor pulmonale with silicosis is often somewhat lower than in emphysema, as seen in this patient; the normal arterial oxygen saturation is unusual for cor pulmonale with congestive heart failure, but is more likely in nonspecific fibrosis or sarcoidosis than in emphysema.[8]

Final Impression: Cor pulmonale due to pulmonary fibrosis, possible silicosis.

Case 10. A 31 year old white man was admitted to the Cincinnati General Hospital for study on March 1, 1951 and discharged on March 2, 1951. He was readmitted for study on July 19, 1951 and discharged on July 20, 1951.

History: The patient was known to have had rheumatic heart disease since 1945. He gave a history of intermittent attacks of exertional dyspnea and dyspnea at rest for six years. He had had frank cardiac decompensation on three separate occasions.

Physical Examination: There were accentuation of pulmonic second sound, a faint early diastolic blowing murmur heard to the left of the sternum in the third and fourth interspace, and a loud presystolic crescendo murmur heard at the apex. The diagnosis of mitral stenosis was made. Opinion was divided as to whether the patient had a Graham Steell murmur or rheumatic aortic valvular insufficiency. Two months after the first cardiac catheterization a mitral valvulotomy was performed by Dr. James Helmsworth, with considerable diminution in the presystolic murmur and marked symptomatic improvement. Two months after the operation cardiac catheterization was repeated.

Laboratory Findings: Preoperative and postoperative x-rays are shown in figure 13.

Cardiac catheterization findings were as follows:

	2 Mos. Preop.	*2 Mos. Postop.*	*Normal*
Right atrial mean pressure	0.3	4.6	(0–5)
Pulmonary artery mean pressure	29.4	15.3	(13–17)
Pulmonary artery	45/18	27/9	(18–30/6–12)
Pulmonary "capillary" pressure	19.1	10.6	(6–12)
Resting index	2.28	2.05	(3.1 ± 0.4)
After exercise	2.18	2.32	
Arterial O_2 saturation	90.8%	96%	(94–100%)
Pulmonary arteriolar resistance	211	107	(47–150)
Mitral valve sq. cm.	0.68	1.40	(4–6)

Comment: The right atrial pressure was normal before and after operation, indiçating the absence of right ventricular failure. Pulmonary arterial pressure was elevated before operation and normal after operation. Pulmonary "capillary" pressure was also elevated before operation and normal postoperatively. The cardiac index was not changed appreciably as the result of operation. Arterial oxygen saturation and pulmonary arteriolar resistance became normal after operation. The calculated mitral valve area was doubled after the operation.

Final Impression: Rheumatic heart disease with mitral stenosis.

Case 11. A 39 year old colored man was admitted to the Cincinnati General Hospital on February 17, 1951, and was discharged on March 8, 1951.

History: The patient had been known to be hypertensive for one year, having an average blood pressure of 160/120 mm. of Hg. Four months prior to study he had developed exertional dyspnea and dependent edema.

Physical Examination: Pulse was 120 and blood pressure was 114/84 mm. of Hg. The patient's skin was smooth and there was some tremor. There was disagreement among examiners as to whether the patient's thyroid gland was enlarged. The point of maximal impulse was palpable in the fifth left intercostal space in the anterior axillary line. There was an apical diastolic gallop. There was 1 plus dependent edema.

Laboratory Findings: The x-ray is reproduced in figure 14 and shows marked cardiac enlargement, chiefly left ventricular.

FIG. 13a (*Left*). Preoperative chest teleroentgenogram of case 10, with mitral stenosis showing pulmonary edema, pulmonary congestion and prominence of the pulmonary artery.

FIG. 13b (*Right*). Postoperative teleroentgenogram of the same patient, showing a small amount of pleural effusion in the left base and marked lessening of the pulmonary congestion.

Impression: Because of the normal blood pressure and questionable thyroid enlargement, opinion was divided as to whether the patient's problem was that of hypertensive cardiovascular disease or whether he was suffering from thyrotoxicosis with heart disease resulting chiefly or partly therefrom.

Cardiac catheterization findings were as follows:

		Normal
Arterial O_2 saturation	94.9%	(94–100)
A-V O_2 difference	8.3 vol. %	(4.5 ± 0.7)
Pressures mm. Hg		
Right atrium mean	1.8	(0–5)
Right ventricular end diastolic	3.04	(0–5)
Pulmonary artery	50/24	(18–30/6–12)
Pulmonary "capillary"	16.8	(6–12)

P.C. tracing suggestive of mitral incompetency
Cardiac index = 1.50

Comment: The normal arterial oxygen saturation is not uncommon in uncomplicated congestive heart failure. The greatly increased arteriovenous oxygen difference is common in the low output type of congestive heart failure. Since the heart is pumping a reduced amount of blood and the oxygen consumption of the tissues is unchanged, the tissues must meet their oxygen needs by extracting increased quantities of oxygen from the capillary blood, thus causing the venous oxygen content to be less than normal and therefore producing a wide A-V oxygen difference. The normal right atrial and right ventricular end diastolic pressures indicated the absence of right ventricular failure. The high pulmonary artery pressure was due in part to elevated pulmonary "capillary" pressure, which in turn was indicative of left ventricular failure. The pulmonary "capillary" tracing showed prominent "C" waves suggestive of mitral incompetency, which is not uncommon in left ventricular failure with dilatation of the left ventricle. The low cardiac index is also characteristic of hypertensive or valvular disease with failure and would not ordinarily be seen in thyrotoxicosis with heart failure. After catheterization a radioactive iodine uptake study showed that 72 per cent of the ingested iodine was excreted in 48 hours, thus confirming the finding that the patient did not have thyrotoxicosis.

Final Impression: Hypertensive cardiovascular disease with congestive heart failure.

Case 12. A 28 year old white woman was admitted to the Cincinnati General Hospital on September 18, 1950, and discharged on January 19, 1951.

History: The patient, a bar-maid, was admitted to the hospital September 18, 1950, with a history of having drunk at least six to seven glasses of beer daily for three years. Her diet was deficient in bread and meat. She had developed dependent edema and numbness of the hands and legs four days prior to admission.

Physical Examination: The blood pressure was 150/70 mm. of Hg, pulse was 106, temperature was 99.8° F., and there was evidence of peripheral neuritis. Venous pressure was increased. The skin was warm. There was diastolic gallop rhythm at the cardiac apex. The heart was enlarged to the left and right and the pulmonic second sound was accentuated. There were moist râles at the lung bases. There was dependent edema of the legs and over the sacrum.

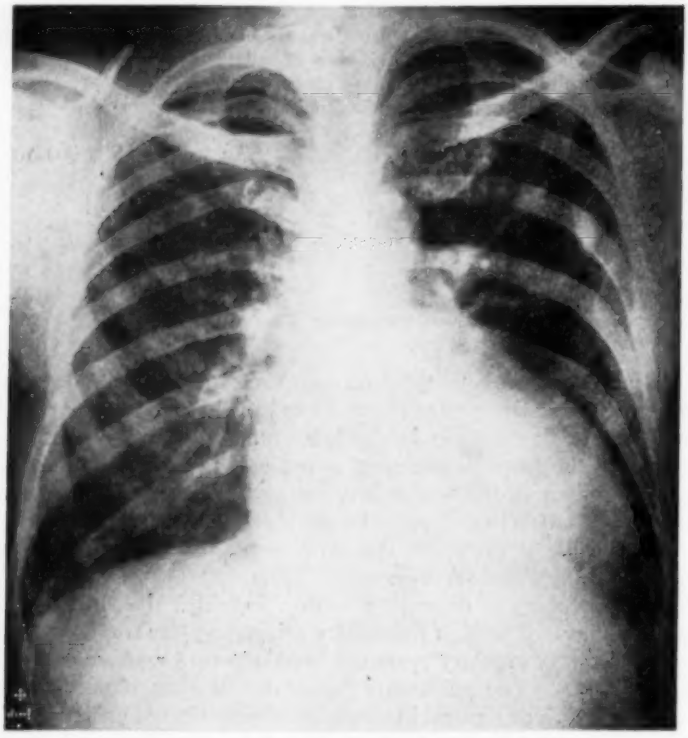

FIG. 14. Chest teleroentgenogram of case 11, showing marked cardiac enlargement, chiefly of the left ventricle.

Laboratory Findings: Hemoglobin was 10.2 gm. and Decholin circulation time was 9.5 seconds, 7.5 seconds and 10 seconds. The electrocardiogram showed only sinus tachycardia and very slight lowering of the T waves. The patient's x-rays are reproduced in figure 15. The first x-ray, taken on admission, shows 25 per cent increase in the transverse diameter of the heart. The second x-ray, taken three months later, shows a normal cardiac silhouette.

Impression: On admission the clinical diagnosis in this patient was that of peripheral neuritis due to thiamine deficiency. When it became apparent that the patient had cardiac involvement, the diagnosis of beriberi heart disease was proposed but was not universally accepted.

Cardiac catheterization findings were as follows:

Pressures mm. Hg	*9/22/50*	*12/29/50*	*Normal*
Pulmonary "capillary"	21.5	8	(6–12)
Pulmonary artery	36/25	21/7	(18–30/6–12)
Right atrium	10.1	3.1	(0–5)
Arterial O_2 saturation	86.6%	93.9%	(94–100)
A-V O_2 difference	3.43	3.09	(4.5 ± 0.7)
Cardiac index	6.09	4.51	(3.1 ± 0.4)

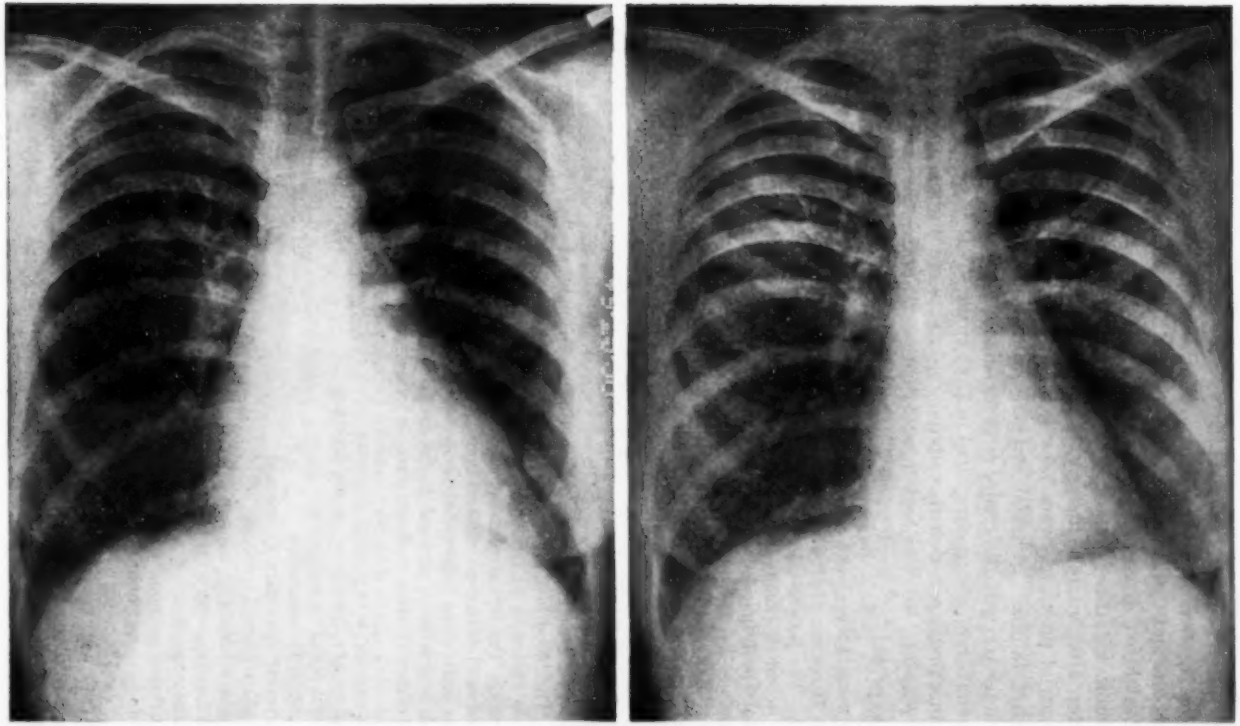

FIG. 15a (*Left*). Chest teleroentgenogram taken one week after admission of case 12. Beriberi heart disease. There is 25 per cent increase in the transverse diameter of the heart.

FIG. 15b (*Right*). Chest teleroentgenogram of the same patient taken approximately four months later, showing the return of the heart to normal size.

Comment: Cardiac catheterization performed four days after admission revealed elevation of pulmonary "capillary" pressure and right atrial pressure indicative of right and left ventricular failure. Arteriovenous oxygen difference was low and cardiac output was high. Both findings were consistent with beriberi heart disease.[9] The anemia was not pronounced enough to be responsible for these findings. Repeated cardiac catheterization three months later, after vitamin therapy, revealed that the pulmonary "capillary" and right atrial pressures were now normal, indicating subsidence of congestive heart failure. Arterial oxygen saturation had risen to normal. Arteriovenous oxygen difference and cardiac index were still abnormal, indicating that complete recovery had not yet ensued. It is possible, in view of the normal pressures, that these latter findings were due to anxiety.

Final Impression: Beriberi heart disease. Subsequent improvement would be expected.

Case 13. A 19 year old colored male was admitted to the Cincinnati General Hospital on December 11, 1951.

History: The patient was admitted for removal of a bone cyst. A cardiac murmur was discovered during the routine preoperative physical examination. There was no history of dyspnea, cyanosis or clubbing. The patient was mentally retarded; otherwise he was asymptomatic.

Physical Examination: Blood pressure was 120/75 mm. of Hg. The general physical examination was negative except for the heart. There was regular sinus rhythm. There was a grade 3 plus systolic murmur heard over the entire precordium, maximal in the second left intercostal space. The heart was not enlarged. The pulmonic second sound was not accentuated and no diastolic murmur was heard. A third heart sound was audible.

Laboratory Data: The electrocardiogram was normal and showed no marked axis deviation. The blood hemoglobin was 14 gm. The chest x-ray was normal and the heart was not enlarged. Cardiac fluoroscopy disclosed slight enlargement of the pulmonary artery. The left atrium and left ventricle were normal.

Impression: Isolated pulmonic stenosis, atrial septal defect or an atypical patent ductus arteriosus were considered as possibilities. The normal electrocardiogram seemed to fit best with an atypical patent ductus arteriosus.

Cardiac catheterization findings were as follows:

Pulmonary artery mean pressure	17.5 mm. Hg
Pulmonary "capillary" mean pressure	11.7 mm. Hg
Right atrial mean pressure	7.8 mm. Hg
Arterial O_2 saturation	94% of capacity
Superior vena cava O_2 content	9.9 vol. %
Right atrium O_2 content	8.5 vol. %
Right ventricle O_2 content	11.8 vol. %
Pulmonary artery O_2 content	11.7 vol. %
Pulmonary flow	5.46 L./min.
Effective pulmonary flow	2.56 L./min.
Left-to-right shunt	2.9 L./min.

Comment: The findings indicate the entrance of blood from the left side of the heart into the right ventricle. In the absence of any evidence of pulmonary insufficiency this would indicate the presence of only ventricular

septal defect, rather than patent ductus arteriosus. There was no evidence of pulmonic stenosis. The possibility of ventricular septal defect was not considered before catheterization because of the high location of the murmur, which was in the second left intercostal space, whereas the murmur of ventricular septal defect is ordinarily maximal in the third or fourth left intercostal space. The x-ray findings were consistent with this diagnosis.

Final Impression: Ventricular septal defect.

Case 14. A 19 year old white man was admitted to the Cincinnati Jewish Hospital on December 27, 1951.

History: The patient apparently had been well until the age of 11 years, when he began to have hemoptysis, exertional dyspnea and cyanosis, followed by clubbing. He had not been a blue baby. He did not squat to relieve dyspnea.

Physical Examination: His blood pressure was 100/70 mm. of Hg in both arms. There was marked cyanosis, with clubbing of the fingers and toes. The heart was not enlarged. There was regular sinus rhythm. There were a grade 5 systolic murmur and thrill, maximal over the pulmonary valve area. The second sound at the pulmonary valve area was faint. No diastolic murmur was heard.

Laboratory Findings: Decholin circulation time was 15 seconds. Red blood count was 8,790,000. Hemoglobin was 21.9 gm. Kline test was negative. The electrocardiogram showed right ventricular hypertrophy. QRS was 0.08 second in duration, P-R interval 0.16 second. Maximal P wave voltage was 1½ mm. in Lead I. In the chest x-ray shown in figure 16 there is a round shadow in the left hilum representing an enlarged left pulmonary artery. There is an emphysematous bulla or cyst in the right mid lung field. Cardiac fluoroscopy showed no intrinsic pulsation in the dilated pulmonary artery. An angiocardiogram was made which is shown in figures 17 and 18. Figure 17 shows the dye entering the right atrium from the superior vena cava; figure 18, taken one and one-half seconds later, shows an opacification of the right atrium and the right ventricle, probably the left ventricle, the left pulmonary artery, and some opacification of the aorta.

Impression: The leading clinical impression was that of tetralogy of Fallot, although the late onset of cyanosis and normal circulation time were against this. It was thought that the angiocardiogram findings could have been due either to an overriding aorta or to a ventricular septal defect with early visualization of the aorta as the result of a right-to-left shunt. Eisenmenger's complex was considered but was thought unlikely because of the faintness of the pulmonic second sound, the absence of a diastolic murmur and the absence of intrinsic pulsation of the pulmonary artery. A measurement of O_2 consumption and CO_2 production at rest and on exercise showed no change in CO_2 production after exercise but a definite decrease in O_2 consumption on exercise, thus favoring the presence of pulmonic stenosis.

Cardiac catheterization findings were as follows:

Pulmonary artery mean pressure	13.3 mm. Hg
Right ventricular blood pressure	160/11
Femoral artery O_2 content	20.5 vol. %
Superior vena cava O_2 content	19.6 vol. %
Right atrium (No. 1) O_2 content	22.6 vol. %
Right atrium (No. 2) O_2 content	20.8 vol. %
Left atrium O_2 content	25.5 vol. %
Pulmonary artery O_2 content	20.1 vol. %
O_2 capacity	29.6 vol. %
Arterial O_2 saturation	69% of capacity

Comment: Figure 19 shows a sudden transition from the mean pulmonary artery pressure of 13.3 mm. of Hg to the high right ventricular pressure of 160/11 mm. of Hg as the catheter tip was withdrawn from the pulmonary artery into the right ventricle. The marked rise in pressure as the catheter was drawn from the pulmonary artery into the right ventricle

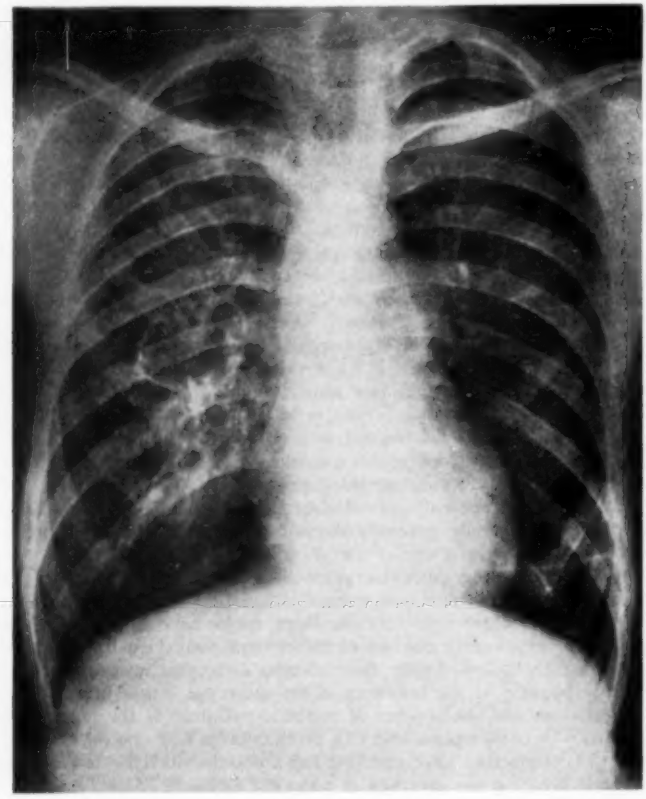

FIG. 16. Chest teleroentgenogram of case 14. Pulmonic stenosis with patent foramen ovale showing normal aortic knob, prominence of the left pulmonary artery with a cyst or bulla in the right mid lung field. The intrapulmonary vascular markings are normal on the right and decreased on the left. The transverse diameter of the heart is not increased.

is indicative of pulmonic stenosis. The catheter tip was advanced through an atrial septal defect into the left atrium. The shunt through the atrial septal defect was chiefly right-to-left, although some left-to-right shunt was also present. The catheter did not enter an overriding aorta. The impression is that the patient has severe pulmonic stenosis with a defect in the atrial septum, probably a patent foramen ovale, with chiefly right-to-left

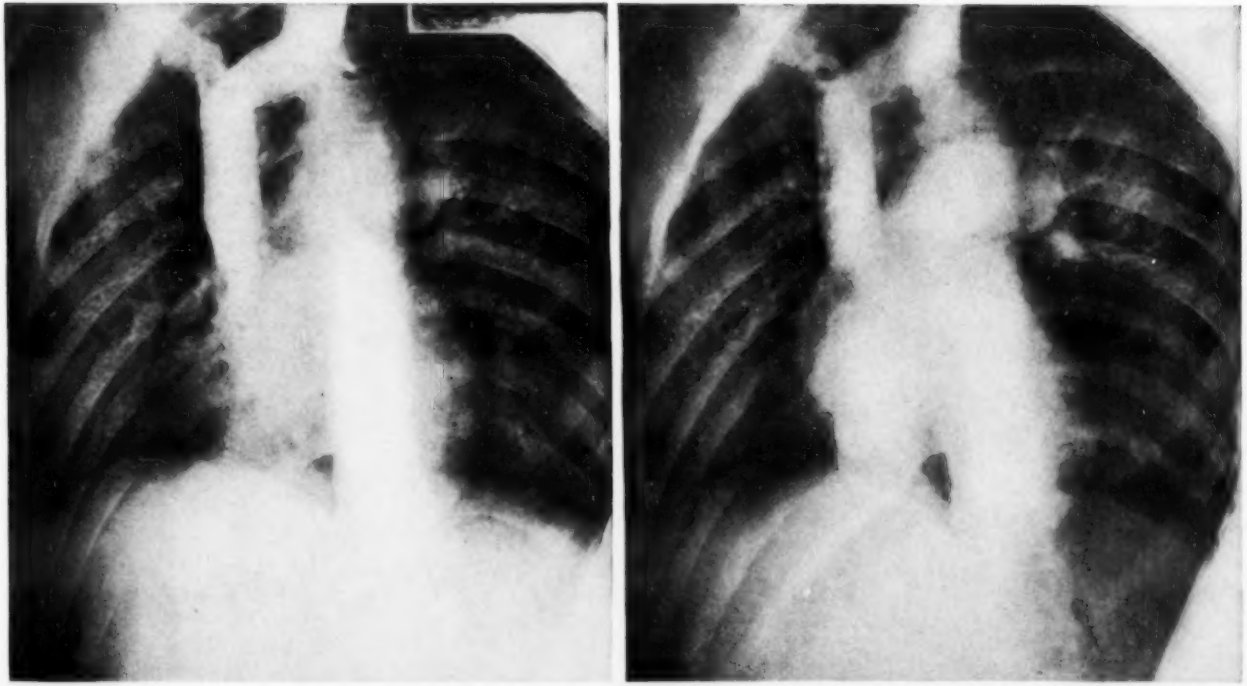

FIG. 17 (*Left*). Chest teleroentgenogram in a series of angiocardiograms in case 14, showing the radiopaque dye entering the right atrium from the superior vena cava.

FIG. 18 (*Right*). Second teleroentgenogram in a series of angiocardiograms of case 14, showing filling of the right atrium, right ventricle and pulmonary artery, with a suggestion of opacification of the aorta and probably left ventricle also.

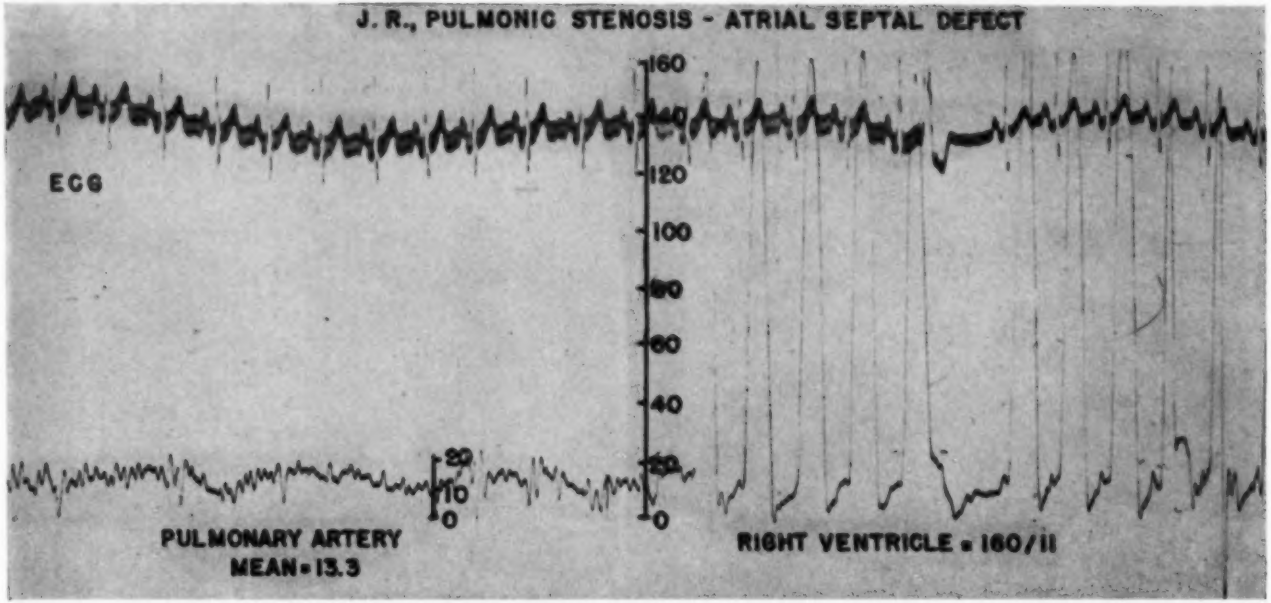

FIG. 19. This is an excerpt from the pressure pulse tracing of case 14, showing an abrupt rise in pressure as the catheter tip was withdrawn from the pulmonary artery into the right ventricle, indicating severe pulmonic stenosis.

intracardiac shunt. In retrospect, the catheter diagnosis of patent foramen ovale and pulmonic stenosis might have been suggested from the history and physical findings if more attention had been paid to the late onset of the cyanosis and to the normal circulation time, which would be opposed to the presence of an overriding aorta, as one would expect in the tetralogy of Fallot. Features of the syndrome described by Taussig,[10] such as pulsating liver, bulging precordium, intraventricular or A-V conduction defects and prominent P waves on the electrocardiogram, were absent in this patient. As stressed by Taussig,[10] the differentiation of this syndrome from the tetralogy of Fallot is important. The Blalock-Taussig operation is generally indicated in the tetralogy of Fallot, but has been followed by congestive failure if

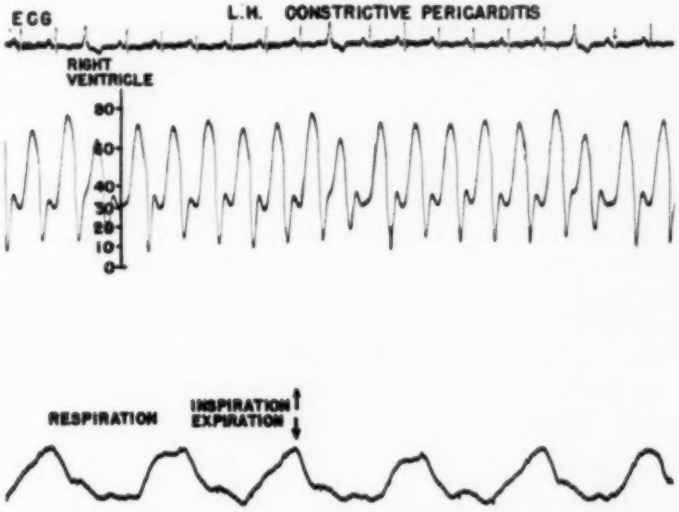

FIG. 20. Simultaneous electrocardiogram, right ventricle pressure pulse and pneumogram of case 15, showing the pronounced diastolic dip and marked elevation of right ventricular diastolic pressure.

employed in this condition. A direct attack on the stenotic pulmonary valve is indicated instead in pulmonic stenosis with patent foramen ovale. This patient is at present awaiting operation.

Final Impression: Pulmonic stenosis with patent foramen ovale.

Case 15. A 48 year old white male was admitted to the Cincinnati General Hospital on October 25, 1951, and was discharged on November 5, 1951.

History: Six years prior to admission the patient developed exertional dyspnea without edema. At that time he was studied and was found to have elevated venous pressure, paradoxical pulse, ascites, hepatomegaly and right hydrothorax. A diagnosis of possible constrictive pericarditis was made. Two weeks prior to the present hospital admission he developed dependent edema and increasing exertional dyspnea.

Physical Examination: Blood pressure was 110/70 mm. of Hg. Pulsus paradoxus was present. The neck veins were distended. There was definite edema of the feet and legs. There were signs of old fibrotic pleurisy. The heart was not enlarged. There was a third heart sound over the precordium. There was no ascites.

Laboratory Findings: The hemoglobin was 13 gm. The electrocardiogram showed sinus arrhythmia, with low voltage of the QRS complex in the standard leads. T waves were of low voltage in the standard and precordial leads. Serum albumin and globulin were normal. Chest x-rays showed bilateral pleural thickening, with calcification of the pericardium. Decholin circulation time was 17 seconds.

Impression: The diagnosis was probable constrictive pericarditis.

Cardiac catheterization findings were as follows:

Femoral artery O_2 content	76.5% of capacity
Arterial CO_2 content	59.3 vol. %
Arteriovenous O_2 difference	5.6 vol. %
Resting cardiac index	2.27 L. per minute
Pulmonary artery mean pressure	46.6 mm. mercury
Right ventricle pressure	65/28
Right atrial mean pressure	24.3 mm. mercury

Comment: In figure 20 the right intraventricular pressure curve of this patient is reproduced, showing the pronounced elevation of the diastolic pressure to about 30 mm. of Hg and a pronounced diastolic dip. Figure 21 shows a paradoxical pulse in the femoral artery of this patient. Figure 22 shows, for contrast, a right ventricular pressure curve in a patient suffering from cor pulmonale with congestive failure. Right ventricular diastolic

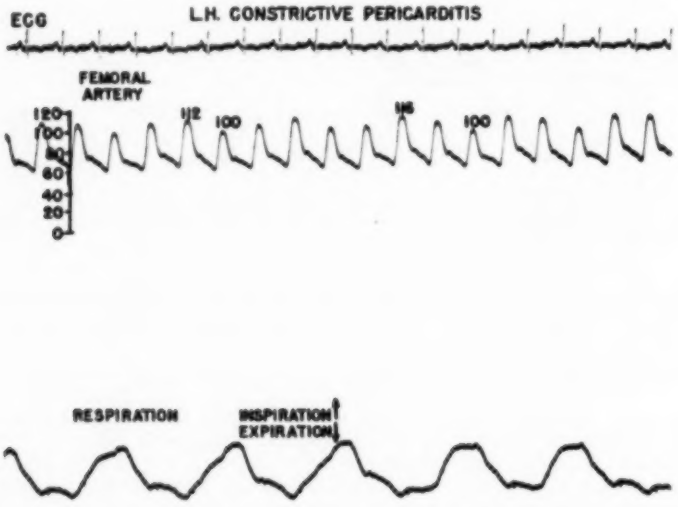

FIG. 21. Femoral artery pressure pulse tracing of case 15, with simultaneous electrocardiogram and pneumogram showing pulsus paradoxus up to 16 mm. of Hg.

pressure is not elevated nearly so much here, and there is no pronounced diastolic dip.

The diastolic dip in the right atrial and right ventricular pressure curves, together with the pronounced elevation in right ventricular end diastolic and right atrial mean pressures, is characteristic of constrictive pericarditis. It has recently been noted that a similar right ventricular pressure curve may be seen in subendocardial fibrosis.[11] The paradoxical systemic arterial pulse is in keeping with this diagnosis, as is the low cardiac index. The arterial hypoxia and hypercapnia suggest that this patient also has a marked degree of alveolar-respiratory insufficiency. In right-sided congestive failure the

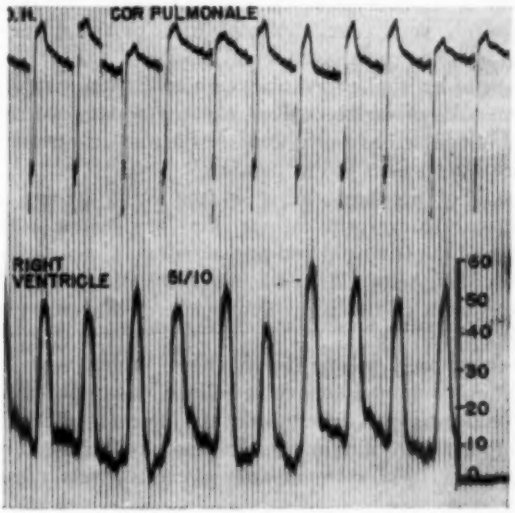

FIG. 22. Right ventricular pressure pulse curve and intraventricular electrocardiogram of a case having cor pulmonale with congestive failure, showing only moderate elevation of right ventricular diastolic pressure and slight, only inconstant diastolic dip.

diastolic dip and diastolic pressure are very rarely of this magnitude. The explanation of this dip, which is seen also in the right atrial pressure curve, is not clear but has been postulated by Hansen and coworkers [7] to be due to the fact that the right ventricular contraction is not impaired in constrictive pericarditis; therefore, the right ventricle is emptied almost normally, lowering the diastolic pressure to near zero. However, markedly elevated right atrial pressure causes rapid ventricular filling, with resultant rise in the ventricular diastolic pressure to a high plateau. The usual case of constrictive pericarditis shows a narrow pulse pressure in the right ventricle. In this case the rather high systolic pressure in the right ventricle is possibly due to the added factor of chronic lung disease, which was present in this patient.

Operation was advised but was refused by the patient. The patient died a few weeks later.

Final Impression: Constrictive pericarditis.

Summary and Conclusions

In our study of adult heart disease we have found cardiac catheterization to be most helpful in the following instances:

1. In the diagnosis of left-to-right shunts, e.g., patent ductus arteriosus, atrial septal defect and ventricular septal defect.

2. The catheter may enter anomalous vessels or pass through congenital defects, e.g., the anomalous pulmonary vein entering the right atrium, persistent left superior vena cava, dextroposition of the aorta, patent ductus arteriosus, and atrial or ventricular septal defects.

3. By means of hydraulic formulae, catheterization may aid in estimating the degree of stenosis of various valves, e.g., pulmonary, mitral and tricuspid. The hydraulic formulae have not been satisfactory in estimating the size of the patent ductus arteriosus in our hands.

4. By means of pressure curves in the right atrium and pulmonary "capillary" pressure curves, the catheter may be of value in the diagnosis of the insufficiency of the tricuspid and mitral valves.

5. The procedure may aid in the diagnosis of right ventricular failure by showing elevation of the right ventricle end diastolic pressure and the right atrial mean pressure.

6. The catheter may aid in the diagnosis of left ventricular failure by showing elevation of the pulmonary "capillary" mean pressure and widening of the arteriovenous oxygen difference, if the failure is of the low output type.

7. The catheter may aid in the diagnosis of high output failure, e.g., in thyrotoxicosis, beriberi, systemic arteriovenous fistula, anemia and Paget's disease of the bone.

8. The catheter may aid in the diagnosis of pericardial constriction and cardiac tamponade by means of characteristic right ventricular pressure curves.

9. Catheterization aids in the diagnosis of cor pulmonale in showing high pulmonary arterial pressure associated with normal pulmonary "capillary" pressure, and a tendency toward normal cardiac output. Pulmonary artery pressure may be expected to rise after digitalization in cor pulmonale with failure, and to fall after digitalization in left ventricular failure.

10. By means of the determination of the oxygen saturation of the pulmonary "capillary" blood, catheterization may be used to differentiate between arterial oxygen unsaturation due to emphysema and that due to right-to-left shunt.

Acknowledgment

The writer wishes to thank Dr. Benjamin Felson, Professor of Radiology, University of Cincinnati, for permission to use the roentgenograms and interpretations. The author also wishes to thank Dr. Richard Westcott and Dr. Ralph Scott for their valuable assistance.

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PSORIATIC ARTHRITIS *

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During the course of examining a group of patients with psoriasis, six cases were discovered with roentgenologic evidence of a peculiar type of arthritis. Four of these cases meet the criteria for diagnosis of the uncommon entity, pure psoriatic arthritis, while two show a mixture which we believe represents a combination of psoriatic arthritis with the rheumatoid type. The association of psoriasis and arthritis will be briefly reviewed and the problem of differentiating psoriatic arthritis from rheumatoid arthritis and other arthropathies will be discussed.

Dermatologists, rheumatologists and radiologists have long been aware of a more than fortuitous relationship between psoriasis and chronic arthritis. While the ordinary sequence of events is psoriasis followed by arthritis, cases have been reported as developing simultaneously,[1] or, rarely, as arthritis followed by psoriasis.[2] Considerable evidence exists for a statistically significant association of psoriasis with an arthritis resembling the rheumatoid type. Psoriasis was present in 2.7 per cent of 300 unselected patients with rheumatoid arthritis and in only 0.7 per cent of 300 nonarthritic controls.[3] Dawson and Tyson [3] reported 26 cases of psoriasis in 1,000 patients with rheumatoid arthritis, and only three cases of psoriasis in a larger group of patients with osteoarthritis. Brunsting [4] and O'Leary [5] reported an associated arthritis of the rheumatoid type in 12 to 15 per cent of all cases of psoriasis. Other authors have found the incidence of arthritis among psoriatics to vary from 0.2 per cent to 25 per cent. Hench, on the other hand, believed that the association of psoriasis and rheumatoid arthritis was merely that of two unrelated diseases appearing in the same person.[6]

Psoriatic arthritis is usually first manifested clinically in the joints of the terminal phalanges. Many observers have noted exacerbations and remissions coinciding with the severity of psoriasis of the nails.[2, 7] Considerable emphasis has therefore been placed on the diagnostic combination of nail lesions and involvement of the terminal joints. Arthritis limited solely to the terminal joints is unusual, however, and in Bauer's series [2] was found in only 26 cases of psoriasis and chronic arthritis. More commonly, there is a generalized arthritis indistinguishable from the rheumatoid type. For this reason Bauer et al. reserved the term psoriatic arthritis for cases with involvement of the terminal joint only. (It must be recognized that marked

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terminal joint involvement may rarely occur in uncomplicated rheumatoid arthritis, and Bauer himself reported one such case.) In an exceptional case the joint lesions in psoriatic arthritis appear distinctive enough to imply a difference in pathogenesis from that of rheumatoid arthritis. Nunemaker and Hartman [8] recently reported a case of so-called pure psoriatic arthritis which manifested chronic psoriasis for at least 10 years before the development of changes in the nail and subsequent arthritis of the terminal phalanges. Even in this case there was a past history of severe "inflammatory rheumatism" at the age of 11, which indicates that a rheumatic diathesis may have preceded the psoriasis.

There are two major theories with regard to the etiology of psoriatic arthritis [9]: one, that the psoriasis produces a "toxin" which causes the joint lesions; the other, that both disabilities result from a common etiologic factor. The facts that the arthritis usually follows long standing psoriasis, that the lesions of psoriasis are frequently adjacent to the affected joints,[10] and that activity in the terminal joints often parallels the extent of the nail lesions,[2, 7] suggest that there is a direct etiologic relationship between the antecedent psoriasis and the arthritis.

Cases 1, 2, 3 and 6 of the following case reports are submitted as examples of what is probably uncomplicated psoriatic arthritis. The fourth and fifth cases represent psoriatic arthritis associated with rheumatoid arthritis.

Case Reports

Case 1. A 29 year old white male salesman developed psoriasis in 1941 with the appearance of a few lesions on the chest. By 1945 the condition had become more extensive, and for the first time he complained of pain in the right fourth toe. Since then the psoriasis had become gradually more severe, with persistent pains in the toes of both feet and some pain and stiffness in the ankles, knees and fingers. Past history was negative with reference to arthritis. The patient was hospitalized in a Veterans Administration hospital in November, 1949. The physical findings there were similar to those described below.

The most recent physical examination, in August, 1951, was not remarkable with the exception of the skin and extremities. Typical lesions of psoriasis involved the face, trunk and extremities. The nails of both hands were moderately involved. The lower extremities exhibited a solid area of erythematous scaling, with extensive involvement of the toes and toenails. The distal third of both feet presented a slight bluish discoloration. There was marked swelling in the interphalangeal joint of the right great toe.

Roentgen examination of the feet (figure 1) revealed destruction along the articular surfaces of several of the interphalangeal and metatarsophalangeal articulations, with narrowing of the joint spaces, periarticular swelling and subarticular haziness or sclerosis representing a diminution in the blood supply to the involved bone. At least two of the joints involved had progressed to the telescoping stage. Similar changes were seen about the interphalangeal joint of the left thumb. Roentgenograms of other major joints were within normal limits. The roentgenograms of the feet showed a lack of the generalized osteoporosis in the involved joints that one would expect if this were rheumatoid arthritis of six years' duration. The

changes, however, cannot be distinguished from those seen in neurotrophic joints or other connective tissue diseases.

Case 2. A 39 year old white male police officer first developed psoriasis in 1942, and by the time of his first Army hospitalization in 1945 there was characteristic psoriasis involving the scrotal area, scalp, and nails of the fingers and toes. The lesions persisted with moderate severity. In 1949, at least seven years after the onset of the psoriasis, swelling, stiffness and redness developed in the fingers of both hands. Past history was negative with reference to arthritis.

FIG. 1. *Case 1.* Note the destruction about the interphalangeal joint of the right great toe and the telescoping of the fourth metatarsophalangeal and proximal interphalangeal joints. Increased density in the subarticular areas, rather than bone atrophy, has been the rule in the cases reported.

FIG. 2. *Case 2.* The distal interphalangeal joints of the thumb, index and middle fingers of the right hand show punched-out areas of erosion, narrowing of the joint spaces, subarticular increased bone density and periarticular swelling.

The most recent physical examination, in December, 1951, revealed the typical lesions of psoriasis involving the scalp, elbows, lower back, buttocks, scrotum, left thigh and nails of the fingers and toes. The distal phalanges of the fingers and thumbs of both hands, except the fourth and fifth on the left, were moderately red and swollen. Apart from these findings, the remainder of the physical examination was not remarkable. Routine laboratory studies, including uric acid determinations, were within normal limits.

Roentgenograms (figure 2) revealed punched-out destructive areas and subarticular haziness about the articular surfaces of the distal phalanges of the thumb, index and middle fingers of the right hand. No true bone atrophy was present. Roentgenograms of the right foot revealed a similar picture in the distal interphalangeal joint of the fifth toe. Roentgenograms of the left hand and foot and other representative major joints were within normal limits.

Case 3. A 35 year old white male clerk first developed psoriasis in 1942 while in military service. The disease began on the abdomen and gradually spread so that by the time of discharge, in 1945, there were scattered patches over the trunk and extremities and moderate involvement of the fingers and toenails. Symptoms of arthritis first appeared about the time of discharge, with pain and stiffness in the toes of both feet. By the end of 1945, the distal joints of all the fingers and toes became swollen and have remained so until the present time. There have been no other joint symptoms or other significant complaints. There was no past history of rheumatism.

The most recent examination, in June, 1952, was not remarkable except for the skin and the joints of the hands and feet. There were a few typical psoriatic plaques on the elbows, right knee and trunk, and moderate psoriatic involvement of the fingernails and toenails. The distal interphalangeal joints of the fingers and toes were all moderately swollen and red.

Roentgen examination of the feet (figure 3) showed evidence of a destructive arthritis involving most of the distal interphalangeal joints and a few of the proximal interphalangeal joints. There was a moderate subchondral sclerosis about the involved joints but no demineralization. Similar changes involved the distal interphalangeal joints of several fingers on both hands (figure 4). The lumbosacral, sacroiliac and other representative joints were normal.

Case 4. A 26 year old white male restaurant manager first developed psoriasis in 1945. Beginning as a small patch on the crown, it gradually became more extensive so that by 1948 there were scattered lesions over most of the trunk and extremities. By 1949 the toenails became affected, but the fingernails, with the exception of the right little finger, remained free of lesions. There was no previous history of rheumatism. Arthritis first appeared about December, 1949, with pain and swelling in the left great toe, followed in about six months by similar symptoms in the right great toe and in the remaining toes of the left foot. During this period there was a definite increase in the severity of the psoriasis, with both new lesions and extension of the old. However, the patient did not note any increase in severity in the psoriasis of the toenails at this time. Because of these symptoms, together with arthralgia in the left hip and left knee, the patient was studied in a private hospital in August, 1950. Two courses of ACTH brought relief of the pain in the hip and knee but had little effect on the symptoms in the toes. The psoriasis was not significantly affected except for relief of itching.

At the most recent examination, in August, 1951, the patient complained of some aching in the left hip and knee and pain in the right great toe and in all the toes of the left foot. Physical examination was not remarkable with the exception of the skin and joints. There were scattered typical patches of psoriasis on the scalp, forearms, trunk, abdomen, genitalia and thighs. The toenails were moderately involved. No skin lesions were in the area of the left hip or knee. There were moderate redness and swelling of the left second and fourth toes. The right great toe was moderately swollen and red, especially in the interphalangeal joint. Routine laboratory studies, including uric acid determinations, were within normal limits.

Films of the left foot (figure 5) revealed destructive changes about the base of the distal phalanx of the left great toe along the articular surface, with periarticular swelling and subarticular increased bone density. More extensive involvement was

noted in the head of the fourth and fifth metatarsals. Roentgenograms of the right foot showed similar involvement of the interphalangeal joint of the great toe. Both sacroiliac joints showed typical changes of atrophic arthritis.

Case 5. A 47 year old salesman first developed psoriasis in 1944, beginning with

FIG. 3. *Case 3.* All of the distal interphalangeal joints show the typical thornlike appearance of psoriatic arthritis. There is early involvement of the fourth and fifth proximal interphalangeal joints. Comparison with noninvolved joints clearly demonstrates the subchondral sclerosis (see arrows).

lesions on the hands and feet, including the nails. Fingernails and toenails subsequently have been destroyed and regrown at least four times. There was no previous history of rheumatism. Both feet became painful and swollen several months after the onset of the psoriasis. Pain in the fingers and backache also appeared at this time

and persisted until the present. During several periods of hospitalization all laboratory studies, including uric acid determinations, were within normal limits.

At the most recent examination, in September, 1951, physical abnormalities were limited to the skin and joints. There was slight psoriatic involvement of the fingernails and toenails, and insignificant lesions on the dorsa of both feet, penis and right

FIG. 4. *Case 3.* Distal interphalangeal joint involvement similar to those seen in figure 2, case 2. Note, again, the subchondral sclerosis and the absence of generalized osteoporosis.

knee. The distal phalanges of the thumb and fingers of both hands were swollen and red. All the toes were red and swollen and in a cock-up position. The lumbar curve was flattened and there was restricted motion in the lower spine. Other major joints revealed no abnormalities.

Roentgen examination of the feet (figure 6) revealed generalized demineralization

of the right great toe, with punched-out areas of destruction in the interphalangeal joint. This toe does not show the characteristic bone sclerosis seen in the other figures. The right hand showed destructive changes in the base of the proximal phalanx of the index finger and subchondral sclerosis at the distal end of the middle phalanx of the middle and right fingers (similar to changes seen in figure 2). Both ankles showed destructive arthritis about their internal aspects, with diffuse surround-

FIG. 5. *Case 4.* Typical changes in the fourth and fifth metatarsophalangeal joints and interphalangeal joint of the left great toe.

ing osteoporosis suggestive of rheumatoid arthritis. There were typical atrophic changes involving the sacroiliac and lumbosacral joints.

Case 6. A 35 year old white male clerk first developed psoriasis in 1945, beginning in the scalp, fingers and toenails. The lesions have remained essentially unchanged ever since. Arthritis first appeared two and one-half years later, with pain and swelling in the terminal joints of several fingers on each hand. There have never been symptoms in any other joint, and there was no past history of rheumatism.

The most recent physical examination, in May, 1952, was not remarkable with the exception of the skin and joints. There were moderate scaling of the scalp, a few insignificant lesions in the umbilicus and on the scrotum, and slight involvement of the finger- and toenails. The terminal joints of the right little, middle and index fingers and left ring and index fingers were moderately swollen.

FIG. 6. *Case 5.* Involvement of interphalangeal joint of the great toe without sclerosis and with generalized osteoporosis in the interphalangeal and metatarsophalangeal joints. However, the roentgenograms of the hands in this case show changes identical to those illustrated in figure 2.

Films of the hands showed a destructive arthritis and subchondral sclerosis involving a number of the distal interphalangeal joints similar to those illustrated in figure 4. Roentgenograms of the feet were normal except for early destructive changes in the left first metatarsophalangeal articulation. All other major joints were within normal limits roentgenologically.

Discussion

Summarizing the six cases, cases 1, 2, 3 and 6 approximate the criteria for so-called pure psoriatic arthritis. Each had a history of psoriasis of long duration preceding arthritic symptoms by from two to six years. In none was there an antecedent history of rheumatism. In each, arthritic changes on roentgenograms were limited to the hands and feet and showed a distinctive type of destructive arthritis involving the phalangeal joints.

Cases 4 and 5 presented similar histories and similar distinctive changes in the distal phalanges of the feet or hands, but, in addition, other joints were involved with typical atrophic arthritis.

We believe that the destructive lesions of the fingers and toes in either the pure or the complicated cases, while not diagnostic of psoriatic arthritis (similar changes may be seen in certain stages of neurotrophic arthritis or in various chronic connective tissue diseases, such as scleroderma or dermatomyositis), are not those ordinarily seen in rheumatoid arthritis of considerable duration. Except for the feet in case 5, none of the involved areas showed the generalized demineralization commonly seen in long-standing rheumatoid arthritis. The distal interphalangeal joint changes in the hands and feet of all cases are distinctly unlike changes seen in rheumatoid arthritis.

These distinctive roentgen changes vary with the stage and extent of joint involvement. In early stages there is a joint effusion; later, there are narrowing and irregularity of the joint surfaces.[11] Osteoporosis is often found early in the disease process, but as the disease progresses the bones show increased density, followed by erosion of the involved joint surfaces, producing a thornlike appearance of the fingers or toes [12] (figures 3 and 4). Finally, joint destruction may be so great as to result in telescoping of the digits [12] (figure 1). Apparently the findings in the cases presented here are not quite so advanced as those in descriptions by Markovits,[13] Schlionsky and Blake [14] and Jungman and Stern,[1] but the nature of the changes is the same and cannot be distinguished from neurotrophic arthritis or arthritis produced by chronic connective tissue disease. Klenk [15] and Nunemaker and Hartman [8] recently reported cases of "pure" psoriatic arthritis similar to those seen by us.

From a study of these six cases and similar cases in the literature, one would be inclined to accept the diagnosis of psoriatic arthritis as a separate disease unrelated to rheumatoid arthritis, and resembling certain types of neurogenic arthritis or the arthritis sometimes seen in chronic connective tissue diseases. The arthritis may be secondary to chronic infection adjacent to the joint or associated vascular changes, or both. Such an etiology has been suggested as the cause of a similar phalangeal arthritis seen in some cases of diabetes mellitus.[16] This theory is consistent with the time relationship and parallelism between the severity of the psoriatic involvement of the fingers and toes and that of the underlying arthritis noted both in our cases and in the literature.[2, 7]

The theory is somewhat compromised by finding typical clinical and roentgenological evidence of psoriatic arthritis in the presence of clearcut rheumatoid arthritis in other joints, as illustrated by cases 4 and 5. An easy solution is to explain the whole picture on the basis of atypical rheumatoid arthritis. One is hard pressed, however, to dismiss the different clinical course and the distinctive roentgen-ray lesions as due to rheumatoid arthritis as we know it. The conflict may be reconciled by accepting the concept of psoriatic arthritis and recognizing that in certain of these cases rheumatoid arthritis is superimposed for reasons as yet unknown.

Summary

1. The clinical aspects and roentgenologic manifestations of psoriatic arthritis are discussed.

2. Four cases are presented which approach the criteria for pure psoriatic arthritis, and two which show lesions of both psoriatic arthritis and the rheumatoid variety.

3. Psoriatic arthritis may be differentiated roentgenologically from rheumatoid arthritis.

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THE THERAPEUTIC RESPONSE OF TUBERCULOUS NEGROES WITH THE SICKLE CELL TRAIT*

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TUBERCULOSIS in the Negro race is more often acute and more often leads to death than in the white race. This is true even when environmental factors are similar in both races.[1] Therefore, constitutional factors must be important in the Negro's reaction to tuberculous infection.

These constitutional factors are not easily defined and their influence is not readily measured in most cases. However, the sickling phenomenon, which is almost peculiar to the Negro, requires only a simple test to uncover its presence. Since blood supply is important in inflammatory diseases such as tuberculosis, it seems reasonable that sickling of red cells may play a part in the tuberculous inflammation of some Negroes.

The sickling phenomenon is seen in patients with sickle cell anemia and, more commonly, as a hematologic characteristic in Negroes with the sickle cell trait. Negroes with sickle cell anemia die of tuberculosis more often than Negroes without sickle cell anemia.[2] In many ways the difference between sickle cell anemia and the sickle cell trait is a quantitative rather than a qualitative one. With respect to the effect of oxygen tension and pH on the formation of sickle cells, there is no clear-cut demarcation between the red cells of patients with sickle cell anemia and the red cells of Negroes with the sickle cell trait.[3] Therefore, just as there is a relationship between tuberculosis and sickle cell anemia, there may well be a similar, though less obvious, relationship between tuberculosis and the sickle cell trait.

Some textbooks of hematology contain statements that the sickle cell trait has no clinical significance.[4, 5] On the contrary, it is conceivable that the sickle cell trait may influence certain diseases in a subclinical manner under certain conditions. This concept may be of some importance, since approximately 7 per cent of American Negroes exhibit the sickle cell trait.[6]

CLINICAL MATERIAL

In a previous paper, Weiss and Stecher [7] reported that the sickle cell trait was found in 19 (or 12.6 per cent) of 150 tuberculous Negroes at the Philadelphia General Hospital. In contrast, only eight (or 5.3 per cent) of 150 nontuberculous Negroes exhibited the trait. In the group of 150 tuberculous Negroes, the 19 sicklers were compared to the 131 nonsicklers. It was found that three fourths of the sicklers and only one third of the nonsicklers

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had an acute exudative form of pulmonary tuberculosis. In addition, two of the sicklers had miliary tuberculosis. Therefore, only three of the 19 cases with the sickle cell trait (16 per cent) had chronic forms of pulmonary tuberculosis, compared to 81 of the 131 cases (62 per cent) without the sickle cell trait. These differences were statistically significant.

In comparing the sicklers with the nonsicklers, there were no differences in average age and sex distribution. The average hemoglobin on admission to the hospital was the same in both groups, emphasizing the point that the sicklers were individuals with the sickle cell trait rather than sickle cell anemia. The sicklers were ill for a shorter time prior to admission than the nonsicklers, and more of the sicklers had fever on admission. *When the sicklers were compared only with those nonsicklers who had acute exudative pulmonary tuberculosis, there were no significant differences.*

The conclusions reached in our previous report were as follows: The sickle cell trait is more than twice as common in Negroes with tuberculosis as in Negroes without tuberculosis; most sicklers develop an acute exudative form of pulmonary tuberculosis; the sickle cell trait has clinical significance and is a factor in the reaction of some Negroes to tuberculous infection.

The Response to Therapy

The purpose of this paper is to present a report on the response of these patients to tuberculosis therapy. The disposition of all 150 tuberculous Negroes is given in table 1 (approximately one year after they were tested for the sickle cell trait). The mortality rate is highest among the nonsicklers with exudative tuberculosis, but because of the small number of sicklers the difference in mortality is not statistically significant. With respect to the number of patients still hospitalized and the number discharged or transferred to other institutions, the difference between the sicklers and the nonsicklers with exudative disease is statistically significant ($P < 0.05$). This suggests that exudative tuberculosis does not respond to therapy in the

Table I

Final Disposition of 150 Tuberculous Negroes One Year After They Were Tested for the Sickle Cell Trait

Disposition	Sicklers		Nonsicklers			
			Those with Exudative Tuberculosis		Those with Nonexudative Tuberculosis	
	No.	%	No.	%	No.	%
Discharged or transferred	14	75	15	30	56	68
Still hospitalized	4	20	26	52	19	24
Died	1	5	9	18	6	8
Totals	19	100	50	100	81	100

same way in sicklers as in nonsicklers. This impression, however, is not borne out by a review of the clinical records and roentgenograms of these patients. Since the sicklers did not differ in other ways from the nonsicklers who had exudative tuberculosis, consideration of the response to therapy will be limited to these two groups of patients.

Table 2 presents therapeutic data and results of therapy among those patients who are still living approximately one year after they were tested for the sickle cell trait, covering the period of observation in the Philadelphia General Hospital. There were 18 sicklers and 41 nonsicklers with exudative tuberculosis. The average period of observation was almost the same in both groups. The type of therapy was determined by various visiting physicians who did not know which patients had the sickle cell trait. Consequently, the proportions in each group receiving various kinds of therapy were essentially similar.

With regard to the results of therapy, there were no significant differences in the rate of sputum conversion, the proportion of patients showing various roentgenographic changes, or the proportions classified as having good, fair or poor final results. Therefore, in these small groups of patients the therapeutic response is the same among tuberculous Negroes with the sickle cell trait, most of whom have exudative tuberculosis, as among Negroes with exudative tuberculosis without the sickle cell trait. It may well be, however, that differences in these groups of patients would become apparent if they were followed in larger numbers for longer periods of time.

Discussion

The sickle cell trait, which is found in one out of every 14 Negroes in the United States, has received very little attention as a factor in disease. Most of the literature devoted to this racial characteristic is concerned with the determination of its incidence and its genetics. However, there have been reports of patients who exhibit the sickling phenomenon but who present manifestations that are *not* typical of the classic clinical picture of sickle cell anemia.[8, 9, 10, 11] As a result, the term "sickle cell disease" has been used to include patients with sickle cell anemia and patients who show bizarre symptoms and signs that can be explained by the occlusions of vessels with sickled red cells. It is possible, therefore, that the sickle cell trait, under appropriate conditions, may assume clinical significance and should no longer be looked upon as a subject for mere exercises in statistical incidence.

The clinical manifestations of active sickle cell anemia in crisis are largely due to widespread vascular occlusions rather than hemolysis or anemia. The picture is protean, and the presenting symptoms probably depend on which vessels are involved in the crisis. Oxygen tension and pH are important factors. Red cells of patients with sickle cell anemia respond readily to anoxia and lowered pH by changing into sickle cells. The red cells of individuals with the sickle cell trait are more resistant to these influences.[3]

TABLE II

Response to Therapy of Tuberculous Negroes with the Sickle Cell Trait Compared to Negroes without the Sickle Cell Trait Having Exudative Pulmonary Tuberculosis

	Tuberculous Sicklers		Nonsicklers with Exudative Tuberculosis	
	No.	%	No.	%
No. of patients, excluding those who died	18	100	41	100
Average period of observation (mos.)	18.5		16.7	
Types of therapy				
Chemotherapy	18	100	41	100
Collapse therapy				
Pneumoperitoneum	12	67	28	68
Pneumothorax	2	11	0	0
Major surgery	1	6	8	20
Results of therapy				
Sputum conversion	11	61	20	49
Roentgenographic changes				
Infiltration				
Increase	2	11	2	5
Stationary	1	6	7	17
Decrease	15	83	32	78
Cavitation				
Lost to view	10	56	18	44
Smaller	2	11	13	32
Stationary	3	16.5	5	12
Larger	3	16.5	5	12
Final result				
Good	10	56	19	46
Fair	4	22	13	32
Poor	4	22	9	22

However, it is conceivable that if, in given local conditions in tissue, one adds the anoxia and acidosis of inflammation to the physiologic variations of the red cell environment, then sickling of red cells of subjects with the trait may be precipitated and miniature local vascular crises may result. Local circulatory changes should alter the pathogenesis of the inflammatory disease. In this way the sickle cell trait, ordinarily of no particular importance, may assume clinical significance in relation to other disease states.

SUMMARY AND CONCLUSIONS

The sickle cell trait has definite clinical significance in that it predisposes the Negro to an acute exudative form of pulmonary tuberculosis. The trait, however, does not seem to influence the response of these patients to therapy for tuberculosis.

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WEBER–CHRISTIAN'S DISEASE: A REPORT OF TWO CASES *

By Robert Friedenberg, M.D., F.A.C.P., *Albuquerque, New Mexico*

Originally described by Pfeiffer in 1892, and its nosology more clearly defined by Weber in 1925 and Christian in 1928, chronic relapsing non-suppurative panniculitis must today be considered an infrequently recognized or reported syndrome rather than a rare one. The condition manifests itself more commonly in females than in males. It is seen from infancy to old age but more frequently in the age group from 20 to 40. Although it has recently been stated that it has never been reported in the Negro race,[1] Johnson and Plice in 1949 [2] did report a case of Weber-Christian's disease in a colored man.

Fever of variable degree and duration was first emphasized as a part of the picture by Christian in 1928. However, five of the 44 cases reviewed by Bendel [3] had no definite febrile reaction, and the presence of fever was not ascertained in one case. Hazel and Lamb [4] have described an afebrile course in their patient, and no significant fever was noted in the two cases we are reporting.

The lesions, which may appear singly or in crops, and with or without fever, are slightly tender to the touch, red to purplish in color, raised and nodular in consistency, and vary in diameter from a half to 3 cm. or more. They most commonly appear on the thighs, abdomen, breasts, buttocks, arms and chest. As a rule the lesions do not suppurate, although suppuration has occurred in several cases reported in the literature.[3, 5, 6] Liquefaction and necrosis may also occur. Constitutional symptoms may be mild or severe. The eruption may completely disappear, with remissions lasting from short periods to many years. Frequently, in healing, there is noted a residual dimpling effect in the site of the old nodule, due to fibrous scarring in the subcutaneous tissue.

The histopathologic picture shows infiltration of the fatty tissue with lymphocytes, monocytes and polymorphonuclear leukocytes. Fibrinoid degeneration in the interlobar areas and in vessel walls may be seen similar to that in collagen disease.

As pointed out by Shuman,[7] there are certain histopathologic similarities to Whipple's disease, erythema nodosum, adiposis dolorosa, insulin lipogranulomata and scleroderma. It is believed the process occurs most commonly in the panniculus, but it has been observed also in the peritoneal, periadrenal, pericardial, omental and mesenteric fat. In Shuman's recent review [7] he indicates that, in two cases dying from the disease itself rather than from associated causes, there was widespread fat necrosis and fatty

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infiltration of the liver. In one fatal case reported by Mostofi and Engleman [8] there was involvement of the skin, epicardium, peripancreatic, periadrenal, perirenal and mesenteric adipose tissue, along with hyperplasia of the reticuloendothelial system and bone marrow.

The many possible etiologic factors which have been incriminated in the past have recently been reviewed by Hallahan and Klein.[1] Among the group of suspect precursors the halogen compounds, camphor, insulin and paraffin injections were considered early. Infections, focal or otherwise, although not infrequently associated, have never been directly proved a factor in this disease. Tuberculosis, Hodgkin's disease, renal failure, dietary deficiency, trauma, impairment of fat metabolism and endocrine factors have all been incriminated at one time or another. Its association with the shoulder-hand syndrome was noted in one case. It is interesting to observe that in Bendel's [3] analysis of 44 cases reviewed in the literature up to 1949, 11 cases of tonsillitis were reported as an associated local infection. One of the cases reported by Kennedy and Murphey [9] had had rheumatic polyarthritis in youth, with recurrence at the age of 63, associated with Weber-Christian's disease. More recently, Brudno [10] reported on the development of Weber-Christian's disease during a bout of recurrent rheumatic fever. All these factors lend a certain credence to the concept that the condition represents a systemic reaction of adipose tissue, allergic in nature to a number of different noxious stimuli.

The differential diagnosis of Weber-Christian's disease, which has been reviewed by Hallahan and Klein,[1] includes the asymptomatic lipomatoses as well as Dercum's disease, with lesions which may remain unchanged for years. Erythema nodosum is differentiated clinically by the fact that the lesions do not progress to atrophy.

Erythema induratum (Bazin's disease) similarly displays no atrophy of the fatty tissue, with the lesions breaking down and ulcerating. Tubercle bacilli may often be demonstrated in the lesions. The sarcoid of Darier-Roussy does not regress spontaneously. It should be borne in mind, however, that some workers consider Weber-Christian's disease a variant of this condition. Old injection sites with atrophic scarring may occasionally be confused. Dermatomyositis may require biopsy for differentiation, and, indeed, the possibility of a relationship between the two conditions has been discussed by Kennedy and Murphey.[9] Scleroderma shows much slower tempo in its evolution, with no evidence of pannicular nodules. A type of spontaneous panniculitis described by Rothman and Makar has a symmetrical distribution, with no reddening of the overlying skin and no subsequent dimpling. To complete their differential consideration, Hallahan and Klein include the gummatous lesions of syphilis, metastatic neoplasms and lymphomas.

No form of treatment has as yet proved of consistent benefit except in isolated instances, as where sulfapyridine occasionally has helped for some

reason that is not apparent, as in Duhring's disease. More recently steroid therapy has been tried, without significant effect; in our case, it may possibly even have hindered further the ordinarily poor healing of the biopsy site.

Case Reports

Case 1. This 41 year old married woman was first seen on September 6, 1951, with complaints that a nodular erythematous eruption had occurred in attacks for the previous two years. Each attack was of several months' duration and was accompanied by malaise, pains in the feet and back, and some dizziness. No significant temperature rise was noted by the patient or us during observation. This woman was seen during her third attack. Each recurrence lasted several months, and with subsidence the nodules tended to disappear, with no residual dimpling. The patient

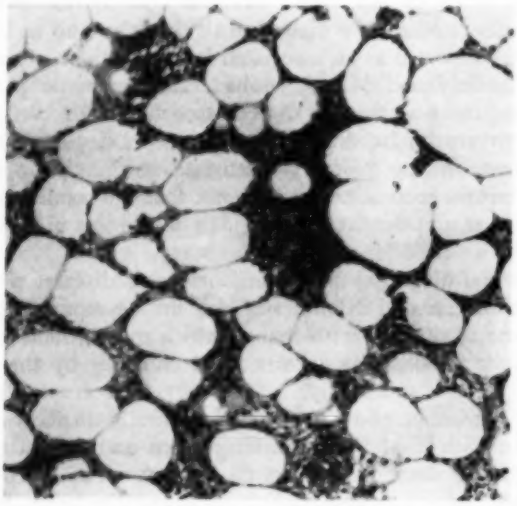

Fig. 1. Nonsuppurative panniculitis (low power magnification) showing the well preserved fat cells.

had been treated in various ways during the previous two years and had had a tonsillectomy shortly after the illness started.

The family history revealed that her mother had died of diabetes mellitus at the age of 68 and her father of cancer of the liver at the age of 73. The patient had two living children, and had had one miscarriage and one stillbirth.

Physical examination revealed nodular erythematous lesions, tender to the touch, scattered over the extensor surface of both legs and on the posterior surface of the buttocks; there was one involuting lesion on the left upper arm in its outer aspect. No dimpling was present. There was no residual pigmentation at the sites of the former involvement, and their locale could be determined only on the basis of the patient's knowledge of their previous existence. Aside from a third-degree retroversion of the uterus, the balance of the physical examination was not remarkable. The patient's blood pressure was 126/84 mm. of Hg. The red blood cells numbered

4,680,000, and the hemoglobin was 12 gm. The white count was 5,800, of which 49 per cent were segmented polymorphonuclear leukocytes, 3 per cent stab forms and 48 per cent lymphocytes. The sedimentation rate was 11 mm. in one hour (Westergren). A urinalysis revealed a specific gravity of 1.011 and a pH of 7. No albumin or glucose was present. Microscopic examination revealed a few epithelial cells.

A diagnosis of relapsing nonsuppurative panniculitis was entertained and the patient was advised to submit to biopsy. Examination of the biopsy material by Dr. A. J. McQueeney revealed "the epidermis is intact and uniformly well-differentiated with moderate flattening of the rete and slight hyperkeratosis. Throughout the superficial and mid-dermis there is perivascular infiltration by small numbers of lymphocytes and mononuclear phagocytes. Dermal collagen appears well preserved and there is no evidence of specific inflammatory reaction or malignancy. Throughout the subcutis moderate numbers of neutrophiles and small numbers of mononuclear

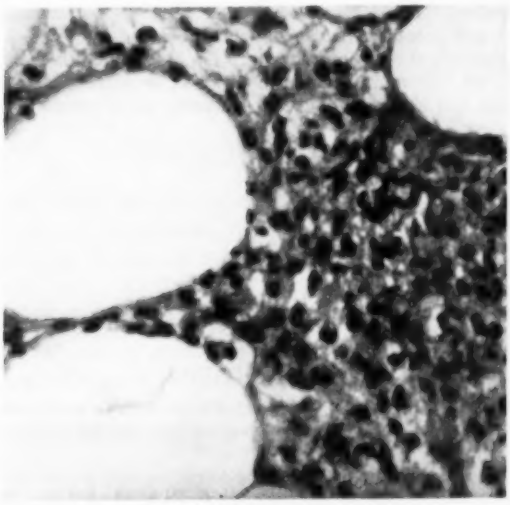

FIG. 2. High power, showing neutrophiles, mononuclear cells and lymphocytes, infiltrating between the fat cells.

phagocytes and lymphocytes infiltrate between the well preserved fat cells." (See figures 1 and 2.)

The patient was placed on Cortone therapy, but this was stopped after one week because of the breaking down of the biopsy incision. The wound was indolent in healing but is intact at present.

Through the courtesy of Dr. F. H. Hanold, of the Santa Fe Hospital, we cite an additional case:

A 29 year old Spanish American male was admitted to the Santa Fe Hospital on September 4, 1950. He had been under observation since March, 1950, for firm, deep-seated erythematous nodules on both legs. These had appeared in episodic crops, the patient having had attacks in 1941, 1949, and again in 1950. The longest episode had lasted two months. The lesions had been noted on the legs and trunk and, on regression, had left a slightly pigmented dimpled area. No systemic or con-

stitutional symptoms had been noted. One nodule was present on the right arm. Two biopsy specimens, examined by Dr. A. E. Margulis, revealed "a widespread inflammation of the fat in both specimens, of similar nature. In the first specimen much of the inflammation is concentrated at the dermal subcutaneous junction and spilled over into the dermis. The inflammation is patchy. In such areas there is loss of fat cells and replacement by a fairly dense exudate in islands and bands. Exudate also invades the septa between the fat cells. In some areas there are quite a few leukocytes but in most areas the inflammation appears more granulomatous and consists principally of macrophages sometimes quasi-epithelioid with an admixture of lymphoid cells and a few plasma cells. Where vessels are caught in the lesion their walls are infiltrated by similar cells but there does not seem intrinsic vascular disease at a distance from the main lesion. In the heart of the lesion fibrous tissue bands apparently replace the fatty tissue where this has been destroyed."

On January 3, 1951, the patient was hospitalized with infectious hepatitis. He had the usual course in this disease, with elevated thymol turbidity and cephalin flocculation tests and increased serum bilirubin. Blood cytology, Wassermann and heterophil agglutination tests were negative. By May, 1951, the cephalin flocculation test was normal; the thymol turbidity was 10 units in August, and in October, 1951, the bromsulphalein test showed 1 per cent retention at 45 minutes, with a 5 mg. per kilo dose.

Summary

Two additional cases of relapsing nonsuppurative panniculitis are added to indicate further that this disease is an infrequently recognized or reported syndrome rather than a rare one. The clinical and pathologic features of the condition are briefly reviewed. The likelihood that Weber-Christian's disease represents an allergic systemic reaction to a variety of noxious stimuli is again suggested.

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A STUDY OF 23 CASES OF REITER'S SYNDROME*

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THE recent treatment of rheumatoid arthritis with hormones has stimulated interest in a group of similar conditions of unknown etiology. Among the latter is Reiter's syndrome, characterized by the occurrence of urethritis, conjunctivitis and arthritis.

During the past five years 23 young adult white males with the clinical picture of Reiter's syndrome have been observed in the Minneapolis Veterans Administration Hospital. Our observations concerning the epidemiology, etiology and therapy of the disease do not agree with many statements in the literature concerning Reiter's syndrome. For that reason the present report has been prepared.

CLINICAL MATERIAL AND METHODS

Since the etiology of Reiter's syndrome is unknown, the selection of cases for this report was based on arbitrary diagnostic criteria. The 23 patients were selected from a larger group having a similar illness but lacking one or more of the usual diagnostic features. It seemed desirable to exclude all cases which were questionable. Twenty of the 23 patients had all three cardinal features: urethritis, conjunctivitis and arthritis. The other three showed little evidence of either urethritis or conjunctivitis but did have arthritis and typical mucocutaneous lesions.

The patients were investigated thoroughly by bacteriologic and other laboratory aids, including, in most cases, cultures of urethral exudate and joint fluid for pyogenic bacteria, gonococci and pleuropneumonia-like organisms. The blood and feces were usually cultured for pathogens. Serologic tests for syphilis and gonococcic complement fixation tests were routine. Roentgenograms of the involved joints were taken in all cases and repeated at intervals during the course of the disease. Electrocardiograms were obtained in most cases.

RESULTS

The essential clinical data in the 23 patients are presented in table 1. All the patients were white males; their ages ranged from 21 to 41 years (median, 31 years). Fever, urethritis, conjunctivitis, arthritis and lesions of the skin and/or mucous membranes were present in most of the patients.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

TABLE I

Clinical Data in 23 Patients Having Reiter's Syndrome

Patient Age	Symptoms and Signs					Last Sexual Exposure, in Days	Previous Similar Episodes	Hospital Stay, in Days	Course
	Fever	Urethritis	Conjunctivitis	Arthritis	Mucocutaneous Lesions				
1. W. R. 22	+	+	+	+	+	41	0	74	Recovered
2. D. C. 21	+	+	+	+	+	? Wife only	1	108	Recovered
3. F. J. 22	+	+	+	+	+	7	0	194	Recovered. Residual hammertoe
4. E. P. 1st Episode 32	+	+	+	+	+	7	0	67	Recovered
2nd Episode	±	+	+	+	+	8	1	79	Recovered
5. K. L. 31	+	+	+	+	+	? Wife only	0	119	Recovered
6. L. K. 28	+	+	+	+	±	9	0	85	Recovered
7. H. D. 35	+	+	0	+	+	5	0	62	Recovered
8. R. P. 41	+	+	+	+	+	? Wife only	0	94	Recovered
9. W. B. 32	+	+	+	+	+	16	1	62	Recovered
10. E. N. 29	+	+	+	+	+	15	1	44	Recovered
11. M. S. 32	+	± Erythema urethral meatus	+	+	+	? Wife only	0	57	Recovered
12. R. M. 28	±	+	0	+	+	12	0	3	Transferred to Navy hospital
13. H. W. 32	+	+	+	+	+	7 Wife only	0	308	Slow recovery. Residual stiff knee
14. J. C. 37	+	+	+	+	+	14	3	120	Recovered
15. H. S. 29	+	+	+	+	+	21	0	72	Improved
16. W. D. 30	±	+	+	+	+	2	0	56	Recovered
17. G. S. 34	±	+	+	+	±	28	6	83	Recovered
18. H. R. W. 23	±	+	+	+	+	?	0	51	Recovered
19. R. L. 32	+	+	+	+	+	14	0	84	Recovered
20. D. N. 28	±	+	+	+	+	10	3	57	Recovered. Hydronephrosis
21. E. O. 39	±	+	±	+	+	? Wife only	6	14	Improved
22. P. N. 30	+	+	+	+	+	? Wife only	2	31	Recovered
23. A. H. 35	+	+	+	+	+	? Wife only	?	51	Improved

There was considerable variation, however, in the severity and duration of these manifestations.

The fever was usually intermittent and low grade (100° to 101° F.), and in only one patient did it reach 103° F. The duration of fever in the hospital in 17 febrile patients varied from four to 113 days (median, 42 days). Fever was seldom a primary complaint. Only transient mild fever was recorded in six patients. None had shaking chills.

The initial symptom was urethritis in 61 per cent of the patients; this was soon followed by conjunctivitis and arthritis. Conjunctivitis was present at the onset in three and arthritis in six of the 23 patients. Eight

of the latter nine patients soon developed urethritis; in one (case 11 in table 1), the only evidence of urethritis was erythema of the urethral meatus. Urethritis usually was accompanied by dysuria, urinary frequency and nocturia. The urethral discharge varied from scant to copious, and was either mucoid or frankly purulent. Four patients had gross terminal hematuria. The urethritis persisted about one month in most cases (range, three to 165 days).

Genitourinary abnormalities were not confined to urethritis. There was evidence of prostatitis in several patients. In one patient (case 18, table 1), cystoscopic examination revealed acute cystitis with reduced bladder capacity. This subsided within a month. Intravenous pyelography in this and one other patient (case 20 in table 1) revealed bilateral hydronephrosis with dilated kidney pelves and ureters. In the former patient the hydronephrosis disappeared completely within six weeks.

Ocular involvement in the main was restricted to a mild or moderate conjunctivitis, usually bilateral. There was injection of the palpebral and bulbar conjunctivae with a purulent discharge. The conjunctivitis was minimal or absent in three patients. In most there was a tendency for it to wax and wane, with complete disappearance after an average course of 75 days (range, seven to 775 days). Four patients had more than one episode of conjunctivitis. More serious ocular lesions occurred in five cases. Three developed marginal corneal ulcers, which healed promptly with little or no residual scar. Two patients had iridocyclitis. This was benign in one, but the other patient had six attacks, eventually leading to the formation of several posterior synechiae.

Objective arthritis was present in every patient; it was the principal cause for hospitalization and led to prolonged disability. The joints most commonly involved, in order of decreasing frequency, were the knees, ankles, wrists, shoulders, spine and hips. The joints of the hands, feet and digits were less commonly involved. The elbows, temporomandibular, sternoclavicular and sacroiliac joints were seldom affected. Although fleeting arthralgia was often the only manifestation of involvement in some joints, in every case before the disease subsided, several joints became tender, stiff and swollen. Often the joints were hot and red. Tenosynovitis was observed in only three patients. Sweating about the inflamed joint was frequent. Considerable joint effusion was common in the knees. The swelling of the other joints, however, appeared to be due to enlargement of the periarticular tissues. The arthritis usually progressed in a migratory fashion and its distribution was often asymmetrical. Although the pain and objective changes might last only a few days in some joints, in the more severely involved joints the arthritis usually persisted for several months, with exacerbations and remissions. As shown in table 1, the hospital stay of the 22 patients whose treatment was completed at the Minneapolis Veterans Hospital ranged from 14 to 308 days (mean, 90 days).

Muscular atrophy adjacent to severely involved joints was common; the muscles of the thighs and calves often became weak and thin as a result of disuse. Residual deformity of the joints, however, was rare. One patient (case 3 in table 1) was left with a hammertoe deformity, and several complained of intermittent stiffness and swelling of involved joints during convalescence. Residual limitation of motion was usually minimal and crepitation absent.

Mucocutaneous lesions were present in all of the patients (table 1). Involvement of the genitalia was most frequent. The most prevalent lesion was a small, erythematous papule, often surmounted by a vesicle. After rupture of the vesicle the ulcerated papule was covered by a purulent crust or a cornified layer. Several such papules were found upon the prepuce and/or the glans penis in 18 of the 23 patients. The corona and shaft of the penis were less often involved. Occasionally erosion of the urethral meatus was present. An erythematous, weeping, eczematoid eruption of the scrotum and groin was seen in four patients. Pruritus was seldom noted.

The next most frequent eruptive lesions were found in the oral cavity. These began as vesicles surrounded by a zone of erythema. The vesicles soon ruptured, leaving small ulcers having an erythematous areola and often coated with a thin, gray-white membrane. They were found upon the palate or buccal mucosa of 48 per cent of the patients. Five patients had similar lesions upon the tongue; loss of the papillae often gave the tongue a "relief map" appearance. These lesions were often painless.

Involvement of the nails was frequent; five patients showed changes in fingernails and five in toenails. In some this amounted only to distal splitting of the nails into several opaque layers. Two patients also had hemorrhages under the nails. In others the nails were converted into thick, horny appendages which eventually separated from the nail bed and were shed in their entirety.

Five patients developed dermal lesions morphologically indistinguishable from those of keratoderma blennorrhagica. The eruption in these patients involved the genitalia, groins, perineum, buttocks, extensor surface of legs, knees, elbows, soles of the feet, axillae and scalp. The earliest lesion was a vesiculated red papule. This was soon covered by a flat, cornified crust which often became thick and horny. After several weeks the papules slowly faded away and the crusts were shed. The nails usually were involved. The exfoliation of the epidermis of the fingers and toes and the changes in the nails had a striking resemblance to certain epidermal mycoses. The dermal and nail changes also simulated those seen in chronic psoriasis.

Other less frequent symptoms and signs were also observed: (1) Anorexia and weight loss of more than 10 pounds were noted by six patients. (2) Nausea and vomiting rarely occurred. (3) Diarrhea was noted by only five patients. In none of the patients was the bowel disturbance char-

acteristic of bacillary dysentery. The diarrhea occurred only during the early course of the disease; in three the stools contained no pus, mucus or blood, and the diarrhea subsided within a few days. One patient had two brief episodes of diarrhea with bloody stools early in his illness. (4) Respiratory symptoms were infrequent. There were three patients who had a cough; one of these had pleuritic chest pain and two had audible moist râles. (5) Functional systolic cardiac murmurs were detected in five patients. (6) Lymphadenopathy was notable in four instances, with the most marked enlargement occurring in the cervical and inguinal regions. (7) The liver was palpable in two patients. Splenomegaly was not noted in any. (8) External otitis and intercostal neuritis were unusual complications occurring in single patients.

Certain epidemiologic data strongly suggest that this may be a venereal disease with the urethra as the portal of entry. Fourteen patients admitted a recent extramarital sexual exposure prior to the onset of their disease. One patient (case 4 in table 1) was observed during two episodes of Reiter's syndrome, the second episode beginning six months after cessation of the first. In each instance this patient admitted extramarital sexual exposure to the same female about one week prior to the onset of his disease. The girl was examined and was found to be free of gonococci by smears and cultures. It is also interesting that in only one instance was a patient aware of the presence of any genitourinary disease in his sexual partner. The time interval between the last sexual exposure and the onset of symptoms was known in 15 patients and varied from two to 41 days (median, 13.5 days). As mentioned earlier, the first symptom was urethritis in 14 of the 23 patients.

There were a few observations which cast some doubt upon the venereal theory. Eight patients denied recent sexual exposure to any persons other than their wives. Analysis of this portion of the problem was at times obscured by a history of exposure to more than one partner. The fact that the initial symptom was not urethritis in nine patients has already been mentioned. Eight of these patients, however, soon developed frank urethritis.

The prolonged course of the disease has already been commented upon. Arthritis proved to be the most persistent manifestation in most cases. There also was a tendency for relapses or re-infection to occur, not only with arthritis but also with urethritis and conjunctivitis or iritis. As shown in table 1, nine of our patients gave detailed accounts of previous illnesses which undoubtedly were due to Reiter's syndrome. They had suffered from one to six such episodes prior to the illness leading to their present hospitalization. Previous diagnoses had included Reiter's syndrome, gonococcic arthritis (not proved bacteriologically), Stevens-Johnson syndrome, rheumatoid arthritis and rheumatic fever. The time interval between attacks varied from one month to four years. As previously mentioned, in one instance (case 4 in table 1) two attacks of Reiter's syndrome occurred with a

six months' interval; each followed shortly after sexual exposure to the same female. We have recently seen a patient (case *22* in table 1) whose Reiter's syndrome began in 1943 while he was with the U. S. Navy at Oran, North Africa. His first symptom was diarrhea without melena. The diarrhea lasted 45 days and was attributed to amebiasis by his physician; the patient denied recent sexual exposure. He has had three attacks of arthritis in eight years (1943, 1946 and 1951).

The results of pertinent laboratory tests are presented in table 2. Where several determinations of the common hematologic data were available, only the admission values are given. The admission hemoglobin value was less than 13 gm. per 100 c.c. in nine patients. The anemia was never severe and usually normocytic and normochromic or slightly hypochromic. A leukocytosis over 10,000/cu. mm. was present in all but five patients; the increase was predominantly in neutrophils. Four patients had an early, mild eosinophilia, and eight patients had more than 5 per cent eosinophils in their peripheral blood at some time during their illness. The erythrocyte sedimentation rate was increased at some time in every patient, and appeared to be correlated with the activity of the arthritis.

Urinalysis disclosed moderate albuminuria in nine patients; pyuria was present in all but one. Significant hematuria was found in three. In two instances the hematuria could be attributed only to urethritis and prostatitis. A third patient with hematuria had, in addition, cystitis and bilateral hydronephrosis, plus hydroureter (case 18 in tables 1 and 2). Another patient (case 20 in tables 1 and 2) had bilateral hydronephrosis, yet his urinary sediment contained only a few leukocytes.

The pertinent bacteriologic and serologic data also are given in table 2. Twelve of the patients had blood cultures and they were sterile. The urethral and/or prostatic exudate was examined for gonococci by smear and culture in all but two instances. In only one patient (case 10 in tables 1 and 2) were gonococci recovered. In 1947 this patient had had typical Reiter's syndrome which was not gonococcal. In 1949, 15 days after extramarital sexual exposure, he developed arthritis followed by urethritis and conjunctivitis. The urethral exudate contained *Neisseria gonorrhoeae*. After one intramuscular injection of 400,000 units of penicillin, gonococci could no longer be recovered. Despite further penicillin for 13 days, he had a protracted illness typical of Reiter's syndrome, including papulovesicular lesions on the palate and glans penis as well as subungual hemorrhages and extensive thickening of several toenails.

Urethral or prostatic exudate was examined by culture for pleuropneumonia-like organisms in eight patients, and in only one (case 21 in table 2) were such organisms found (figure 1).* Joint fluid was studied for gonococci in seven patients without success, and in two, cultures for pleuropneumonia-like organisms also failed to show growth. Smears and cultures of

* The culture medium was veal infusion agar plus 50 per cent horse serum.

conjunctival exudate in five cases yielded only staphylococci and diphtheroids. Cultures of skin lesions in three patients showed no pathogens. Feces cultures in the five patients with transient diarrhea failed to reveal Shigella or other pathogens.

TABLE II

Laboratory Data in 23 Patients Having Reiter's Syndrome

Patient	Hgb gm.%	WBC	Diff. % Pmn./ % Lymph.	ESR mm./ 1 hr.	Urine	G.C.* Comp. Fix.	Culture				X-Rays of Joints
							Urethra		Joint		
							G.C.†	P.L.‡	G.C.†	P.L.‡	
1. W. R.	11.5	13,700		86	ManyWBC	0x1	0x3	0x1			Osteoporosis
2. D. C.	12.0	11,300	82/18	100	FewWBC	0x2	0x4	0x2	0x1	0x1	Normal
3. F. J.	11.0	14,000	85/12	100	ManyWBC 3+ Alb.	0x2 +x1 0x4	0x1		0x1		Periostitis. Osteoporosis
4. E. P. 1st Episode	13.6	10,050	72/23	50	ManyWBC 1+ Alb.	0x1 +x2 0x3	0x2		0x2		Slight osteoporosis
2nd Episode	14.9	5,500	55/37 7% Eosin.	50	ManyWBC 1+ Alb.		0x4				Normal
5. K. L.	13.8	10,700		31	ManyWBC Tr. Alb.	0x2	0x4				Osteoporosis
6. L. K.	14.0	12,000		29	ManyWBC	0x3	0x1				Normal
7. H. D.	13.5	10,700		70	ManyWBC RBC 1+ Alb.	+x1 0x2	0x2				Osteoporosis
8. R. P.	11.5	10,900	80/18	106	Few WBC 1+ Alb.	0x4	0x1	0x1	0x1		Periostitis. Osteoporosis
9. W. B.	12.7	12,450	81/18	108	Few WBC	0x4	0x4		0x1	0x1	Osteoporosis
10. E. N.	17.3	11,100		4	ManyWBC	0x3	+x1 0x6	0x2			Slight osteoporosis
11. M. S.	14.4	12,700	81/16	75	Few WBC 1+ Alb.	0x3	0x1	0x1			Normal
12. R. M.	14.4	12,200	83/15	37	Few WBC ManyWBC 2+ Alb.	0x1	0x3				Normal
13. H. W.	12.7	17,150	73/22	86	ManyWBC	0x1	0x1		0x1		Old osteochondritis, periostitis, osteoporosis
14. J. C.	15.1	12,450	79/20	47	ManyWBC	0x1	0x2				Normal
15. H. S.	11.3	11,150	68/26 6% Eosin.	118	Few WBC	0x1	0x2				Osteoporosis
16. W. D.	13.5	14,400	75/23	67	Few WBC	0x6			0x1		Periostitis, osteoporosis
17. G. S.	14.3	11,200	64/32	50	ManyWBC	0x2	0x2				Osteitis
18. H. R. W.	17.0	5,900		32	Gross RBC ManyWBC 4+ Alb.						Normal
19. R. L.	13.3	11,300	79/11	68	ManyWBC 2+ Alb.	0x1	0x3				Slight osteoporosis
20. D. N.	12.2	9,750	66/26	72	Few WBC	0x2	0x2				Normal
21. E. O.	12.9	7,950	60/30 4% Eosin.	25	Few WBC	0x1	0x1	+x1			Osteoporosis
22. P. N.	15.6	7,150	75/20	26	0	0x1	0x2	0x1			Eburnation
23. A. H.	15.1	13,350	61/34 5% Eosin.	47	ManyWBC	0x1	0x3	0x1			Normal

*G.C. Comp. Fix. = Gonococcus complement fixation. Result and no. of examinations.
† G.C. = Gonococcus, smear and culture. Result and no. of examinations.
‡ P.L. = Pleuropneumonia-like organisms, culture. Result and no. of examinations.

Serologic tests for syphilis were negative in every patient. The gonococcus complement fixation test was performed in all but two patients. The latter was consistently negative in 19 patients, including the sole patient (case 10 in table 2) from whose urethra gonococci were recovered. As

shown in table 2, three patients (cases 3, 4 and 7) had transiently positive gonococcus complement fixation. In none did the positive test persist. Shigella agglutinin titers were not determined.

Electrocardiograms were taken in 20 patients and were normal in 14. Transient abnormalities found in the tracings of the remainder consisted of T wave abnormalities in four, ST segment displacement in two, ventricular premature contractions in two, and prolonged PR interval or widened QRS complexes in one patient each.

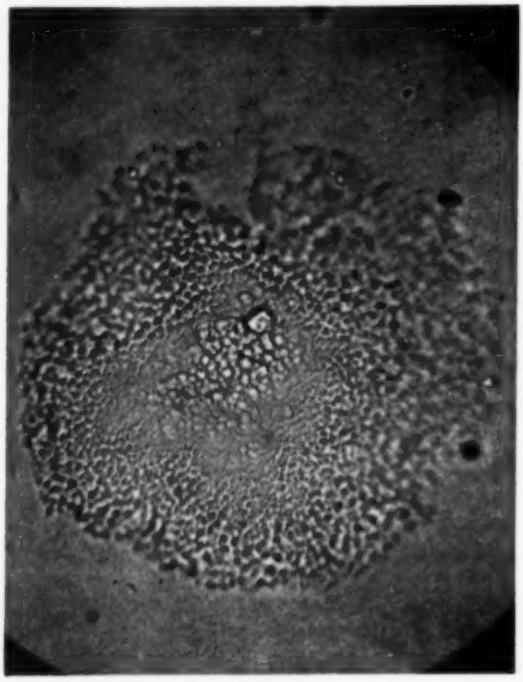

FIG. 1. Colony of pleuropneumonia-like organisms on veal infusion agar containing 50 per cent horse serum; the organism was recovered from the urethral exudate of a patient with Reiter's syndrome (case 21 in tables 1 and 2).

A battery of liver function tests was performed in six patients and revealed only abnormal cephalin cholesterol flocculation in three. Renal function studies were normal in five patients, except for delayed excretion of phenolsulfonphthalein dye in two. The blood uric acid concentration was tested and found normal in six patients. Spinal fluid examination in a patient having involvement of upper thoracic vertebral articulations revealed no pleocytosis but the protein concentration was 92 mg. per 100 ml. Biopsies of hyperkeratotic skin lesions in six cases were interpreted by com-

petent pathologists as indistinguishable from keratoderma blennorrhagica.

Although three patients had a cough, only one had pulmonary lesions demonstrable by roentgenogram; the latter had transient peribronchial infiltrate in the right lower lobe consistent with bronchopneumonia. Cardiac enlargement was not observed in any patient. As indicated in table 2, roentgenograms of the joints revealed no abnormalities other than soft tissue swelling in eight patients. Osteoporosis of variable degree was observed in 14. Periostitis occurred in four, usually adjacent to joints actively inflamed. Destructive changes were found in the joints of only two patients. In one of the latter (case 17) there was cartilage destruction in two metatarsophalangeal joints. The patient was left with a hallux valgus upon recovery. Another patient (case 13 in table 2) had osteochondritis of the right knee prior to the development of Reiter's syndrome; several loose particles of cartilage had been removed surgically. During the course of

TABLE III

Results of Therapy in 23 Patients Having Reiter's Syndrome

Drug	Dose	Duration	No. of Patients	Results
Sulfadiazine	6 gm. oral/day	7–21 days	8	No benefit
Penicillin	300,000–6,000,000 units I.M./day	2–31 days	18	No benefit
Streptomycin	1–3 gm. I.M./day	7–16 days	6	Slight improvement in ½
Aureomycin	2 gm. oral/day	6–14 days	8	No benefit
Chloramphenicol	2 gm. oral/day	14–16 days	2	No benefit
Cortisone	75 mg. I.M. or 25–300 mg. oral/day	7–60 days	3	Temporary improvement in all
ACTH*	80 mg. I.M./day	4, 15 and 21 days	3	Temporary improvement in ½

* Pituitary adrenocorticotropic hormone, Armour & Co., Chicago, Ill.

the Reiter's syndrome this knee became severely inflamed, as was the interphalangeal joint of the left thumb, injured shortly before by a blow with a hammer. Roentgenograms of the knee and thumb revealed periarticular cystic degeneration of the bone along with some cartilage destruction. The thumb returned to normal upon convalescence, but the destructive changes in the knee remained. It was not certain that the Reiter's disease had increased the amount of damage already present.

The results with various therapeutic agents have been summarized in table 3. No benefit was observed with sulfadiazine, penicillin, aureomycin or chloramphenicol in doses adequate for the treatment of susceptible infections. There was no significant change in fever, arthritis or mucocutaneous lesions. The use of streptomycin (1 to 3 gm. intramuscularly daily) for seven to 16 days, however, was followed by a significant decrease in fever, joint pain and inflammation in four out of six patients. The im-

provement was never dramatic, and two patients failed to improve in any way.

Recently a few patients have been treated with hormones. Three patients, given 75 to 300 mg. of cortisone daily for seven to 60 days, experienced a temporary incomplete remission of fever and arthritis during therapy. When the cortisone was discontinued, however, the patients returned to their pretreatment condition. Pituitary adrenocorticotropic hormone (ACTH) was given to three patients in a dose of 20 mg. intramuscularly four times daily for four to 21 days. A moderate decline in fever and arthritis was noted in one patient, but relapse occurred as soon as treatment was stopped. The other two patients obtained little relief.

Several other agents were used without success. These included Mapharsen, colchicine, triple typhoid vaccine and hyperthermia in a fever cabinet. Symptomatic improvement of the arthritis was achieved through the use of bed-rest, salicylates and physiotherapy. No attempt was made to treat the urethritis locally. When conjunctivitis was severe or iritis was present, the eyes were treated with rest, mydriatics and mild antiseptics. Oral mucosal lesions seldom required any local therapy. Moist skin lesions seemed to dry and heal more quickly with frequent applications of Vioform powder. A high-caloric, balanced diet and intensive physiotherapy were regarded as essential in the treatment. All the patients recovered with little residual damage to their joints or other structures, but convalescence was usually slow and relapses were frequent. To illustrate the course of the disease in its severest form the following case report is given.

Case Report

F. J., a 22 year old white unmarried farmer, was admitted to the Minneapolis Veterans Hospital June 22, 1947. Late in April he had developed a purulent urethral discharge one week after sexual intercourse. His local physician found no gonococci upon smear of the exudate, and penicillin did not alleviate the urethritis. About May 10 the conjunctiva of the right eye became inflamed, and two days later his right ankle became red, swollen and painful. He was immediately hospitalized elsewhere and given sulfadiazine. The left ankle, knees, hips, neck, fingers and shoulders soon were involved. There was no diarrhea at any time. After three weeks penicillin was given and fluid was aspirated from the knees. The patient had daily fever and his arthritis continued unabated. He lost 50 pounds in weight. He was therefore transferred to the Minneapolis Veterans Hospital.

Physical examination revealed a slender, seriously ill young man with a temperature of 100.4° F. The eyes were normal but both external auditory canals were injected. The mouth was normal. The cervical spine could not be moved without pain. Somewhat tender lymph nodes were palpable in the posterior cervical region, both axillae and groins. There were musical râles throughout both lungs. The heart was normal. The liver was palpable but the spleen was not. An erythematous, ulcerative, vesicular eruption was noted on the glans penis and prepuce. A small amount of pus could be expressed from the urethra. The prostate was boggy and tender. Both shoulders, the right sternoclavicular joint and interphalangeal joints of the left hand were tender and swollen. Both hips were stiff and painful. The knees were swollen; the right knee was fluctuant. The ankles were swollen and

stiff. The thigh muscles were very atrophic. The wrists were swollen and showed evidence of tenosynovitis. Most of his physicians at this time thought that he had gonorrheal arthritis.

Initial laboratory studies included the following: Urinalysis showed many leukocytes and occasional erythrocytes. His hemoglobin was 11.8 gm.; erythrocytes, 4,020,000, and leukocytes, 6,700 per cubic millimeter, with a differential count of 68 per cent neutrophils, 30 per cent lymphocytes and 2 per cent eosinophils, and sedimentation rate 112 mm. in one hour. Stained smears and/or cultures of the blood, feces, joint fluid, skin lesions and urethral exudate revealed no pathogens (including gonococci and Shigella). The gonococcus complement fixation test was negative

FIG. 2. Keratoderma of the skin of the feet of a patient with severe Reiter's syndrome. Patient F. J. (case 3 in tables 1 and 2) on July 17, 1947.

with six out of seven sera examined during the next four months. At the height of his disease (August 25, 1947), his serum calcium was 11.3 mg. per 100 c.c.; phosphorus, 5.9 mg. per 100 c.c., and alkaline phosphatase, 47 King-Armstrong units.

The chest roentgenogram was negative; films of the joints revealed soft tissue swelling. Some of the fingers and the right ankle showed periosteal elevation and proliferation. The ankles also showed considerable osteoporosis, with some cystic changes under the articular surfaces. There was no evidence of cartilage destruction in any joint. An intravenous pyelogram was normal. Electrocardiograms revealed nonspecific T wave changes and a transient first degree atrioventricular heart block.

The patient was put to bed and given a soft diet. Salicylates were given but he continued to have severe joint pain and a spiking fever up to 102° F. On July 3 vesicular, erythematous lesions appeared in the oral mucosa. Aspiration of the right

knee yielded clear yellow fluid containing a few neutrophilic leukocytes and no gonococci. Beginning on July 9, many papulovesicular lesions appeared on the skin of the extensor surfaces of the ankles, lower legs and wrists (figure 2). The lesions had an erythematous base and were 2 to 3 mm. in diameter. A biopsy revealed changes characteristic of keratoderma blennorrhagica. Penicillin was given in doses of 100,000 units intramuscularly every three hours for six days, without improvement. Cultures of prostatic exudate, joint fluid and skin lesions failed to yield gonococci. The diagnosis of Reiter's syndrome was eventually accepted by all consultants. Physiotherapy was given as tolerated. The joints slowly improved with hot packs, massage and whirlpool baths. In the course of one month the skin lesions became brown in color and markedly keratinized (figure 3). Keratinization became so extensive under the fingernails and toenails that they were shed. His balanitis, pyuria and fever continued.

FIG. 3. Keratoderma of the hands and legs of patient F. J. on September 30, 1947.

Beginning on September 27, streptomycin was given in doses of 0.4 gm. intramuscularly every six hours for 10 days. The pyuria diminished and his fever slowly declined. About November 1 he began to gain weight, his arthritis subsided and the keratotic lesions were shed. All mucosal and skin lesions disappeared completely. His anemia was corrected by five 500 ml. whole blood transfusions. By November 22 he was able to sit in a chair, and two weeks later he began to walk. When discharged January 6, 1948, he was afebrile and free of pain and had gained 20 pounds in weight (figure 4).

He was again hospitalized October 27, 1948, for surgical correction of a hammertoe. This was the only residual remaining as a result of his Reiter's syndrome.

FIG. 4. Marked improvement in keratoderma and arthritis of patient F. J. (February 2, 1948), nine months after onset of Reiter's syndrome.

A successful arthrodesis was carried out. There has been no recurrence of symptoms to date.

DISCUSSION

Although there is no doubt that others had earlier described similar cases, chiefly following bacillary dysentery, the first detailed description of the syndrome manifested by our patients was that of Reiter in 1916.[1] His patient,

a German soldier, developed pain in the legs, urethritis, conjunctivitis and polyarthritis but no diarrhea. Gonococci were not found in the urethral discharge, but two months after the onset a venous blood culture revealed spirochetes which he called *Spirochaeta forans*. Reiter called the disease "spirochaetosis arthritica." Subsequent studies have failed to confirm the relationship to spirochetes.[3] The number of patients with this clinical syndrome, however, has become quite large. The literature was thoroughly reviewed by Vallee [2] in 1946 and by Paronen [3] in 1948.

The complete triad of urethritis, conjunctivitis and arthritis has not been present in many of the patients reported elsewhere as instances of Reiter's syndrome. It is indeed probable that all these symptoms need not be present in every case. However, we have chosen to report here only those patients with either the complete triad or arthritis and typical mucocutaneous lesions in the absence of urethritis or conjunctivitis since the etiologic agent is unknown.

It is to be noted in table 1 that urethritis or conjunctivitis was minimal or absent in a few of our patients but arthritis was always rather severe. The exclusive occurrence in males in our series is not surprising, since the patients were all seen in a veterans hospital. Few cases, however, have been reported in females.[3] Practically all authors agree that Reiter's disease is almost exclusively a disease of young adult males, many of whom were veterans of the Armed Forces engaged in the two recent World Wars.[4]

Since prolonged low grade fever is the rule, an infectious agent may well be the cause. The frequent occurrence of urethritis as the initial symptom suggests that the urethra is the portal of entry in the male. The unknown etiologic agent or its products must be widely disseminated throughout the body in view of the widespread lesions. Since purulent lesions are rarely seen in the eyes and joints, it is unlikely that a pyogenic organism, such as the gonococcus, is involved.

The arthritis, though severe and prolonged, is almost always completely reversible. The latter suggests a toxic or allergic genesis. There is no notable tendency for cartilage destruction such as occurs in pyogenic arthritis.

Vesicular and papular lesions in the skin and mucous membranes (table 1) have been so common in our series as to aid in the diagnosis of doubtful cases. Reiter's syndrome should be strongly suspected in any young adult male having acute arthritis of the large joints associated with dermal and mucosal eruptions of the types described, even though conjunctivitis and/or urethritis may be minimal or absent. The vesicular appearance of the eruption has often suggested the possibility of a herpetic viral infection. Inoculation of vesicular fluid into the scarified cornea of the rabbit, however, has failed to produce herpes simplex lesions. The later stages of some dermal lesions are often indistinguishable from those of keratoderma blennorrhagica. The latter condition has been thought to be produced solely by the gonococcus. There can be no doubt, however, that these hyper-

keratotic papules do occur in patients having Reiter's syndrome with no evidence of gonococcal infection.[5]

Reiter's syndrome with vesicular mucosal lesions, subungual hemorrhages and splitting of the toenails into several opaque layers was observed in a patient (case 10 in tables 1 and 2) recently treated successfully with penicillin for acute gonococcal urethritis. This suggested to us that the term "keratoderma blennorrhagica" might be, in a sense, a misnomer. In reality the latter might be due not to the gonococcus but to the unknown agent causing Reiter's syndrome. If the latter is a venereal infection, it is conceivable that some patients might contract a gonococcal infection simultaneously, thus confusing the clinical picture.

"Gonococci" have been isolated by smear from keratotic skin lesions of patients having gonorrheal urethritis, but it is doubtful whether gonococci have ever been cultured from these skin lesions. Keefer [6] has cited evidence that horses repeatedly injected with sterile filtrates of cultures of gonococci may develop keratotic skin eruptions. It seems probable, therefore, that keratoderma is not a manifestation of any one specific infection.

In a recent monograph Paronen [3] has reported a wartime epidemic of Reiter's syndrome in 344 residents of Finland occurring after an epidemic of bacillary dysentery. He found that 96.4 per cent of his patients had had a recent attack of Flexner Shigella dysentery. Only 23.9 per cent of his patients had urethritis as their first symptom. Paronen concluded that Reiter's syndrome occurred only after dysenteric infection. Agglutinins for Flexner A + D + WX bacillus were found in a titer of 1:80 or over in 61 of 132 patients. Stool cultures were performed in 209 patients and in only five patients was he able to recover Flexner's bacillus during the attack of Reiter's syndrome. Stool specimens were examined in only a few cases during the dysentery preceding the attack of Reiter's syndrome. Furthermore, he estimated that only 0.2 per cent of those having bacillary dysentery subsequently developed Reiter's syndrome.

In the series reported here, only five of the 23 patients had diarrhea. Cultures of the feces of these patients revealed no pathogens. We have come to the conclusion that Reiter's syndrome either is not a specific entity or else has no causal relationship to bacillary dysentery. In the light of numerous reports [5] of Reiter's syndrome following shigellosis, it would seem possible that the syndrome may have diverse etiologies. There is such marked similarity in the symptoms and signs from patient to patient, however, that one is strongly tempted to call it a specific entity due to a single cause.

It is clear that this syndrome is not a variant of rheumatic fever or of rheumatoid arthritis, though the latter occasionally may be difficult to differentiate. The eruptive lesions, urethritis and rarity of joint deformity are all unlike rheumatoid arthritis. Furthermore, the arthritis in Reiter's syn-

drome is often asymmetrical and usually does not include the interphalangeal joints. Endocarditis never occurs.

The suspicion that this is often a venereal disease is strong, since 14 of our 23 patients admitted recent extramarital sexual exposure. The lack of symptoms in the female partners and the infrequent occurrence of Reiter's syndrome in women are unexplained. The long incubation period, the lack of gonococci in the urethra or joint fluid and the benign course of the arthritis all serve to differentiate the syndrome from gonococcal arthritis. The lack of consistently positive gonococcus complement fixation tests in our patients and those of others [3] has been an aid in this regard. Nevertheless, the prolonged course of the arthritis is not unlike that of patients having nonsuppurative gonococcal arthritis. The latter patients can be differentiated only on clinical and serologic grounds, since gonococci cannot be cultured from the joints. Toxic or allergic factors may play a rôle both in Reiter's syndrome and in nonsuppurative gonococcal arthritis.

Reiter's syndrome may be difficult to distinguish from some forms of erythema multiforme, particularly Stevens-Johnson syndrome (erythema multiforme exudativum) and Behcet's syndrome (relapsing iritis with ulcers of the mouth and genitals).[7, 8] In both of the latter syndromes there may be arthritis with ocular, genital, oral and skin lesions. There are commonly vesicular and bullous skin lesions along with lesions typical of erythema multiforme. Loss of vision is much more frequent than in Reiter's syndrome, and arthritis is usually absent or only mild. The skin lesions of erythema multiforme are usually sufficiently characteristic to permit ready separation from those of Reiter's syndrome. The etiology is unknown.

Finally, one must consider the possible rôle of pleuropneumonia-like organisms. Dienes [9, 10] and others [11-14] have recovered these organisms from the urethra and joint fluid of several patients having Reiter's syndrome. These organisms also have been isolated from the urethra of men having nongonococcal or abacterial urethritis. Urethral cultures of only one of eight patients we studied were positive (table 2). The rôle of these organisms remains in doubt.

Reiter's syndrome has been treated by most of the available antibacterial agents. As shown in table 3, the only antibiotic producing significant improvement in our patients was streptomycin. Since the degree of improvement was seldom striking, and because of the known toxicity of this drug, it is doubtful whether its use is justified except in the most severely ill patients. Warthin [12] had a somewhat more enthusiastic opinion regarding streptomycin, but he treated only four patients and in some of these the reported benefit seems doubtful. There have been a few recent optimistic reports regarding adrenocorticotropic hormone (ACTH) and cortisone.[19, 20] We have used each of these drugs in three patients but have noted only temporary suppression of the fever and arthritis. The most useful therapeutic measures have been rest, high-caloric diet, salicylates and physiotherapy.

Summary and Conclusions

1. Twenty-three young adult males with Reiter's syndrome have been studied. The frequent involvement of the skin and mucous membranes has been emphasized. The skin lesions may mimic entirely those of keratoderma blennorrhagica. The arthritis was prolonged in duration but rarely produced permanent deformity.

2. Evidence has been presented which suggests that the disease may be due to a venereal infection, with the urethra as the portal of entry.

3. Bacteriologic and serologic studies demonstrated active gonococcal infection in only one of the 23 cases. Pleuropneumonia-like organisms were isolated from the urethral exudate in only one of eight patients examined. Fecal cultures in five patients with diarrhea failed to show Shigella or other bacterial pathogens. The etiology remains in doubt.

4. The most effective therapeutic measures were rest, high-caloric diets, salicylates for pain and intensive physiotherapy. Streptomycin seemed to produce slight improvement in four of six patients. Cortisone and pituitary adrenocorticotropin (ACTH) caused a temporary decrease in the fever and arthritis of a few patients.

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NICOTINIC ACID IN THE TREATMENT OF DEPRESSION *

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A PRELIMINARY report [1] on the treatment with nicotinic acid of 15 patients suffering from various forms of depression shows 14 much improved. This result is of sufficient interest to merit further investigation. The rationale of the procedure lies in the possible association between abnormal mental states and disturbances of cerebral circulation, and it was suggested that measures which lead to vasodilatation also bring about an improvement in the mental state.

The present series, treated at the Manchester Royal Infirmary, is of 16 patients who were consecutive referrals to the University Clinic, November, 1950, to July, 1951. It included five cases of reactive depression, six of cyclothymic depression, and five of menopausal and involutional depression. The schema of oral dosage indicated by Washburne [1] was followed, in 11 cases, viz. 450 to 600 mg. daily for the first week, then 900 mg. daily for two weeks, in divided doses. Treatment was terminated abruptly in the present series, although Washburne used a gradual decline in dosage. No intravenous therapy was given. An inert tablet, indistinguishable from nicotinic acid, was given to five patients. Nine patients of the series were in-patients and seven were out-patients, but apart from this there was no variation in the handling of patients; in particular, no other treatment of any sort was given at the same time except for nightly sedatives when required.

The responses to treatment may be grouped as follows:

(1) Patients who were symptom-free, including three who needed further nicotinic acid after the first course. As a subgroup (1a) were two patients who admitted partial but lasting relief of their symptoms.

(2) Patients who either had no relief from their symptoms, or only temporary relief, and subsequently failed to respond.

In all cases the patient's account was checked by clinical observation while he was in the ward, or, when necessary by reports from relatives.

The results can be tabulated as follows:

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From the Department of Psychiatry of the University of Manchester, England.

	In-Patients		Out-Patients		All Patients	
	Nic. Acid	Placebo	Nic. Acid	Placebo	Nic. Acid	Placebo
Group 1	2	1	1	—	3	1
Group 1a	00	1	1	—	1	1
Group 2	2	3	5	—	7	3
Totals	4	5	7	—	11	5

Comment

For in-patients, therapeutic results tended to be the same for patients treated with nicotinic acid and for those treated with the placebo.

In-patient treatment with a placebo tended to produce better results than out-patient treatment with nicotinic acid.

In considering Washburne's results, attention may be drawn to the following points:

First, out of 29 patients in her series, results of only 15 were published. Some of the 29 were excluded because of "so high a degree of suggestibility that objective evaluation was impossible." The criterion for deciding the presumed lower suggestibility of the published cases is not given.

Secondly, psychotherapy was given in all cases concurrently with the nicotinic acid, but no details of a control series are available. Ten of the 15 patients were admitted for an initial intravenous injection of nicotinic acid (cf. the results obtained by hospitalization alone in the present series).

Lastly, all Washburne's patients were under 48 years of age and, as they were drawn from a student population, it is possible that many were much younger. In the present series, none of the four out-patients and three in-patients over 40 received any apparent benefit from nicotinic acid.

In the introduction to her paper, Washburne refers to several reports on the cerebral circulation and metabolism in schizophrenia, but quotes only one similar investigation [2] in depressive states, which states: "No change in the cerebral blood flow could be demonstrated." It is doubtful how far these results, obtained in schizophrenia, can be usefully applied to depressive states, having regard to the views held on the differing genesis and pathology of the two conditions.

The present investigation does not support the claim that nicotinic acid may be a useful therapeutic agent in the treatment of depression. While these results do not exclude the possibility that this treatment may speed the convalescence in a mild depression in a young person, it would not appear to achieve better results than can be obtained by other and simpler means. No benefit was observed in this investigation in older patients or in those severely depressed.

Summary

1. An investigation into the use of nicotinic acid in the treatment of depression is described.

2. The encouraging results of a previous investigation were not confirmed, and the possible reasons for this are discussed.

3. On the basis of the present series it is concluded that nicotinic acid is not a useful agent in the treatment of depression.

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MANAGEMENT OF INTRACTABLE SPRUE WITH CORTISONE AND ADRENOCORTICOTROPIN (ACTH) *

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In a previous communication,[1a] observations on the clinical and chemical effects of cortisone and ACTH in the sprue syndrome were reported. Independently, similar observations by other authors [1b, 1c] have been published. Of the five patients with primary sprue studied by us, four proved to be resistant to the conventional forms of therapy prior to the use of these hormones.[1a] It is the purpose of this paper to report the results of prolonged treatment and certain additional observations made in the past 18 months. The group studied consisted of the above five patients and three others.

Clinical Characteristics

The eight patients presented here were clinically established instances of primary sprue. They revealed at some time all or most of the typical features of this syndrome, namely, diarrhea, steatorrhea, weight loss, weakness, anemia, polyavitaminosis, hypocalcemia, hypoproteinemia, tetany and osteoporosis. They had no roentgenologic or other evidence of organic disease in the gastrointestinal tract as seen in secondary sprue.[2] Primary sprue has no known etiology, although there is evidence that its development is related to a nutritional deficiency.[3]

The diagnosis of primary sprue in these patients was based upon the history, physical examination, characteristic results of serial examinations of the peripheral blood and bone marrow, and chemical analyses of the serum for proteins, calcium, phosphorus, oral and intravenous glucose tolerance tests, multiple liver and pancreatic function studies, prothrombin time determinations, vitamin A tolerance tests, roentgenologic examinations of the gastrointestinal tract and the skeleton, stool cultures, stool examinations for occult blood, ova and parasites, microscopic estimation and quantitative determinations of fecal fat.

This series of patients consisted of four men and four women whose ages ranged from 28 to 72 years. Seven patients had nontropical sprue; one woman (case 4), a native Puerto Rican, may have represented the tropical form of the disorder. Their most prominent symptoms and signs were weight loss, weakness, anorexia, diarrhea, abdominal distention, stomatitis

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and glossitis. In addition, three patients exhibited tetany (cases 1, 2 and 3 in the tables); two, purpura (cases 1 and 3), and three, edema of the lower extremities (cases 1, 2 and 8). All patients appeared chronically malnourished; their weight loss was marked, ranging from 19 to 73 pounds.

The duration of symptoms varied from one to 20 years, during which time these patients were treated, when indicated, with the generally accepted regimen. It consisted of a high protein diet with restricted amounts of fat and carbohydrates, given primarily as monosaccharides; in addition, crude or refined liver extract, folic acid and vitamin B_{12} were administered for prolonged periods of time in adequate doses in all but two patients. Case 4 was in full hematologic relapse after cessation of liver therapy four years prior to observation, and case 5 had received inadequate liver treatment before institution of hormonal therapy. Whenever indicated, calcium and multiple vitamin preparations, especially vitamin K, were administered orally or parenterally. Tween 80, pancreatin, bile salts, multiple plasma and blood transfusions, and oral antibiotics were used in selected cases, with equivocal results.

Seven of the eight patients reported here exhibited varying degrees of resistance to the therapy outlined above. This was evidenced by persistence of diarrhea, steatorrhea and weight loss. The most consistent therapeutic response was hematologic; there were in some cases improvement in the anemia, disappearance of the megaloblastic arrest and return of the prothrombin time to normal. Despite therapy, seven of the eight patients examined showed an anemia; five of the eight, macrocytosis; five of seven, hypoprothrombinemia; five of seven, hypoalbuminemia; and four of seven, hypocalcemia. The vitamin A tolerance test was flat in the seven patients examined, and the oral glucose tolerance test was flat in seven of the eight patients examined (exception, case 8). The roentgenologic examination of the small intestine revealed a deficiency pattern in all but one patient (case 4). See tables 1 and 2 for a summary of pertinent data.

The possible rôle of the adrenal cortex in intestinal absorption [4] suggested the use of cortisone and ACTH in primary sprue. A trial with these hormones was instituted in the hope that this form of therapy might increase intestinal absorption and/or stimulate a sense of well being and appetite which, in itself, could favorably influence the general condition of these patients.

Outline of Management

Drug Administration: The hormonal treatment of each patient, with two exceptions (cases 5 and 8), was initiated in the hospital. During hospitalization a thorough reëvaluation of their clinical status was obtained prior to the institution of cortisone or ACTH therapy. Because of the necessity for frequent intramuscular injections, treatment with ACTH was limited to hospitalized patients. After discharge from the hospital the therapy was continued exclusively with cortisone.

TABLE I

Clinical and Laboratory Data Prior to Cortisone or ACTH Therapy

Patient	Sex	Age	Nativity	Duration of Symptoms (years)	Weight (pounds)		Diarrhea		Hematologic Findings			Prothrombin Time[a] (seconds)	Serum Calcium (mg. / 100 ml.)	Roentgen Studies of Small Intestine	Remarks
					Previous Highest Weight	Lowest Weight	Stools per Day	Character	Hemoglobin (gm.)	RBC (million)	Bone Marrow Aspiration				
1. V. S.	F	28	U.S.A.	8	116	76	4–14	Watery, tan	12.1	4.2	Normal[b]	120 (11)	7.7	D.P.[c]	Under liver therapy.
2. K. M.	F	59	Ireland	5	147	95	10–12	Watery yellow	11	3.6	Normal	23 (12)	6.3	D.P.	Under liver therapy.
3. S. H.	F	67	U.S.A.	15	120	81	2–3	Watery, tan	8	2.7	Normal	100 (12)	6.6	D.P.	Severe hemorrhagic manifestations on a previous admission, refractory to vitamin K therapy but responded to blood transfusions.
4. C. R.	F	72	Puerto Rico	5	130	97	1	Semi solid, yellow	7.8	2.1	Megaloblastic arrest	12 (12)	9.2	Normal	Stopped liver therapy 4 years ago.
5. H. K.	M	42	England	7	150	131	4–8	Watery to semisolid, tan	13.8	2.5				D.P.	Received inadequate liver therapy.
6. P. S.	M	53	Poland	20	150	110	2–4	Semisolid, tan	12.8	3.6		128 (15)	9.1	D.P.	Severe hemorrhagic manifestations on a previous admission, responded promptly to vitamin K therapy.
7. C.S.	M	35	Canada	1	180	107	4–6	Watery, tan	11	3.8	Normal	43 (13)	9.2	D.P.	See case report.
8. L. D.	M	45	Poland	20	150	118	2–3	Semisolid, tan	16	5.3	Normal	11.5 (11.5)	7.9	D.P.	Under vitamin B_{12} and folic acid therapy; hypoproteinemia for 15 years; steatorrhea, flat vitamin A tolerance curve but normal oral glucose tolerance curve.

[a] The first figure of this column indicates the prothrombin time of the patient. The second figure, in parentheses, is that of the corresponding control.

[b] Bone marrow aspirations were performed after prolonged liver or vitamin B_{12} and folic acid therapy except in case 4.

[c] D.P. indicates deficiency pattern.

TABLE II

Results in 21 Courses of Hormonal Therapy

Patient	Therapy			Weight (pounds)		Stools per Day		Fecal Fat Content[a]		Vitamin A Tolerance Curve		Serum Proteins[b] (gm./100 ml.)	
	Course	Duration (days)	Total Dose (gm.)	Before	Highest After	Before	During or After	Before	During or After	Before	During or After	Before	During or After
1. V. S.	A Cortisone	10	1.0	80	98	3–7	1	40.6(27.8)	+[c]	Flat	Improved	2.5/1.8	
	B ACTH	13	1.0	87	90	2	1	+	+	Flat	Improved		
	C Cortisone	49	2.6	97	112	3	1	+	19.4(10.6)	Flat	Flat		4.6/2.7
	D Cortisone	5	0.5	110	108	6	1	+				3.7/2.6	
	E Cortisone	83	4.5	105	120	2–4	1		26.9(16.0) 41.0(25.8) 43.0(28.9)		Flat		4.5/3.4
	F Cortisone	155	5.3	110	122	4–8	1		39.5(23.6)		Flat	3.5/2.5	3.9/2.5
2. K. M.	A Cortisone	14	1.5	102	100	3	1	+	+	Flat	Flat	3.8[d]	4.8[d]
	B ACTH	17	1.05	92	98	1	1	+	+		Flat		2.2/2.6
	C Cortisone[e]	42	2.5	98	95	1	1	+	36.9(20)		Flat	2.3/2.7	

[a] All values are expressed as percentage of dry fecal weight; the first figure represents the total fecal fat content, the figure in parentheses represents the fatty acid fraction, while the difference between the two figures represents the neutral fat fraction.

[b] The first value indicates serum albumin; the second, serum globulin.

[c] + indicates the presence of steatorrhea observed microscopically.

[d] Value represents total serum protein.

[e] Patient succumbed to a bilateral pneumonia at another hospital one month after cessation of cortisone therapy; postmortem findings were compatible with the diagnosis of primary sprue.

TABLE II—*Continued*

Patient	Therapy			Weight (pounds)		Stools per Day		Fecal Fat Content[a]		Vitamin A Tolerance Curve		Serum Proteins[b] (gm./100 ml.)	
	Course	Duration (days)	Total Dose (gm.)	Before	Highest After	Before	During or After	Before	During or After	Before	During or After	Before	During or After
3. S. H.	A ACTH	16	1.22	91	93	1	1	+	+	Flat	Flat	2.0/1.6	
	B Cortisone	13	0.6	89	89	3	1	+		Flat	Flat		
	C ACTH	35	1.95	82	84	2	1	56.5(39.9) 50.4(37.5)	23.3(17.3) 40.1(26.3) 49.4(39.0)[f]	Flat	Improved	2.2/2.8	4.5/2.5
	D Cortisone	143	6.575	84	100	1	1	34.1(26.7)	45.8(33.9)[g]			3.5/2.5	3.7/2.8
4. C. R.	A ACTH	5	0.5	100	103	1	1	+	+	Flat	Improved	3.8/2.9	4.3/2.4
5. H. K.	A Cortisone	17	1.05	138	145	2–5	1	+					
6. P. S.	A ACTH	28	1.97	108	123	2	1		46.8(27.1)	Flat	Flat	4.1/2.9	4.2/2.4
	B Cortisone	28	1.935	115	122	2–3	1	62.4(23.6)	61.7(24.9)	Flat		4.2/2.5	
7. C. S.	A ACTH	30	2.0	107½	150	3–4	1	46.1(28.4) 40.8(28.3) 33.5(23.9)	28.9(13.5) 11.5(6.8) 21.8(6.4)[h]	Flat	Flat	3.0/2.7	3.6/2.9
	B Cortisone	122	5.1	122	152	3	1	32.5(18.2)	26.5(11.6) 29.3(10.2)	Flat	Improved	3.2/2.3	4.0/2.1
8. I. D.	A Cortisone	63	3.0	139	141	2	1–2	34.3(17.5)	27.7(14.5) 25.4(13.8)	Flat	Flat	2.5/1.6[i]	2.9/1.9
	B ACTH	29	2.15	140½	134[j]	1–2	1	31.1(16.0)	34.4(16.1)	Flat	Flat	2.5/2.1	2.8/1.3

[f] Value obtained on specimen taken 10 days after cessation of ACTH therapy.
[g] Value is an average of six determinations made over a 3½ month period; individual values ranged from 34.7(23.4) to 52.3(44.0).
[h] Value obtained on specimen taken 14 days after cessation of ACTH therapy.
[i] Average of nine representative determinations taken over a 16 year period.
[j] Decrease in weight represents loss of edema fluid clinically present for 16 years.

The initial dose of ACTH was usually 100 mg. daily, given intramuscularly in four equally divided doses. The initial dose of cortisone was usually 100 mg. per day; this amount was divided into one or two doses and administered intramuscularly in five courses of therapy and orally in eight. Patients were maintained at these liberal doses for from one to two weeks, by which time a striking improvement had usually been observed. The dosage was gradually reduced by 12.5 to 25 mg. decrements at weekly or biweekly intervals, depending upon the progressive subsidence of symptoms. In this manner it was possible to reduce the daily dose and to maintain certain patients on a dose as low as 25 to 37.5 mg. of cortisone daily.

Diet: With two exceptions, all of the patients who were given this form of therapy were initially placed on a low fat, high protein, high calorie diet, with the sodium content limited to 500 mg. per day. The two exceptions were ambulatory patients (cases 5 and 8); their salt intake was limited to a minimum but was not determined. However, when patients had improved sufficiently to allow for small maintenance doses of the hormones, the sodium restriction was liberalized to afford a more palatable diet. At this time the restriction of fat and carbohydrate was found unnecessary in several instances, and patients were allowed a free choice of foods. Following a dietary indiscretion, some patients noted on a few occasions a transient episode of diarrhea lasting only a day or two.

Additional Therapy: During the treatment period, the previous antianemic therapeutic regimen was continued in adequate doses. In case 5, adequate antianemic therapy was reinstituted, before hormonal treatment; in case 4 it was reinstituted after a five day course of ACTH therapy, and in case 8, it was given for months prior to but omitted during the course of ACTH therapy. Potassium chloride was administered, when indicated, to patients in amounts of 3 to 6 gm. daily. Patients with hypocalcemia or marked osteoporosis were given calcium in the form of powdered calcium gluconate.

Complications: These patients were examined at frequent intervals in order to detect any untoward effects of hormonal therapy. Repeated intramuscular injections in sprue patients resulted in occasional abscess formation at the injection site, despite uniform aseptic technic. This was probably due to lowered resistance in these patients. The production of a slowly absorbing adrenocorticotropic preparation will, it is hoped, reduce the incidence of this complication and allow its use on an out-patient basis. Studies with a slowly absorbing ACTH preparation in sprue patients are in progress.

Overt tetany was observed on four occasions in three patients (cases 1, 2 and 3) treated with cortisone. It was believed that the hypochloremic alkalosis, associated with hypocalcemia, precipitated these episodes. Ammonium chloride has satisfactorily prevented any recurrences in the one patient with two episodes of tetany, for it has controlled the hypochloremia and the alkalosis and, in addition, has acted as a diuretic. In the other patients, the oral administration of calcium was apparently sufficient.

Infrequently, mercurial diuretics were administered to edematous patients suspected of exceeding their salt limitation; edema, as a rule, appeared only during the first few weeks of therapy, when patients were receiving larger doses of the hormone, and it was then that diuretics were occasionally required. On maintenance doses of cortisone, edema formation was not observed, although patients were allowed unrestricted amounts of sodium.

It should be emphasized that patients with sprue, because of their lowered resistance to infections, must be reëxamined at frequent intervals, since these hormones can alter unfavorably the response to infection and mask the symptoms of such a process.

Response to Treatment

Twenty-one courses of hormonal therapy, 13 of cortisone and eight of ACTH, were observed in eight patients. The duration of cortisone treatment varied from five to 155 days,* while that of ACTH ranged from five to 35 days.

Striking clinical improvement was observed one to three days after the institution of therapy in five patients. In case 4, presenting mainly hematologic signs, a five day course of ACTH did not result in remission, and in cases 2 and 8 the improvement was gradual but limited. There were noted an improved sense of well being and an increase in activity and alertness. An increase in appetite and food intake was reflected in a gain of body weight, especially during the courses of prolonged therapy. Weight gains, as a rule, were more frequent and marked in patients receiving extensive courses of cortisone therapy than in those receiving ACTH treatment. This, however, may have been due to the greater length of therapy with cortisone as compared to ACTH.

Diarrhea disappeared in one to two days, with one exception (case 2), and stools of these patients frequently appeared to have a normal consistency. Steatorrhea, measured by quantitative fecal fat determinations, was present throughout the courses of treatment but was diminished or sometimes absent for varying time periods. It must be realized that the higher dietary content of fat allowed later in the courses of therapy may have been a contributing factor to the higher fecal fat contents.

No changes in the hematologic findings were noted. However, all but two patients continued to receive antianemic therapy, which had resulted in a sustained correction of their anemia. One exception (case 4), who received no antianemic treatment, was in full hematologic relapse, and failed to show any hematic improvement with a five day trial of ACTH administration. She later showed a reticulocyte response to folic acid and vitamin B_{12} therapy. In case 8 the antianemic therapy was interrupted during the four week period of ACTH administration without discernible effect.

The flat oral glucose tolerance tests were essentially unaltered during or after administration of hormonal therapy. The vitamin A tolerance tests revealed improved absorption in two instances of ACTH therapy (courses

* As of December 15, 1951.

1B and 4A) and two instances of cortisone therapy (course 1A and 7B). However, in one course (3C) of ACTH treatment and one of cortisone therapy (3B), the fasting vitamin A and carotene level revealed a significant elevation, although the curve remained flat. This observation suggested an increased but delayed absorption of vitamin A and carotene.

In those patients (cases 1, 2, 3, 7 and 8) in whom hypoalbuminemia was present there often was a decided increase in the serum albumin fraction (see table 2). In cases 1, 2, 3 and 8, with hypocalcemia, a significant increase in the serum calcium level was noted. Sodium and fluid retention, hypochloremia and hypokalemia were noted once in case 2 and twice in case 3. The infrequent occurrence of these complications was probably due to the preventive therapy previously mentioned. Roentgenographic studies of the small intestine were performed repeatedly in six patients; only two (cases 1 and 7) showed significant improvement, while four remained unchanged.

It should be emphasized that the degree of improvement varied with each patient. In five patients it was most striking, with disappearance of diarrhea, substantial increases in weight and the ability to tolerate a normal diet. In two patients it was essentially limited to subjective improvement and reduction in the number of stools, without a gain in weight. In one patient, evaluation was not possible because of the short duration of treatment (five days).

The effects of cortisone and ACTH in a therapy-resistant patient are illustrated in the following case report (case 7) and in the accompanying figures (figures 1 and 2).

Case Report

History: A 35 year old Canadian male was first seen because of crampy lower abdominal pain, diarrhea and a marked weight loss over a period of seven months. He had never lived in a tropical climate, and gave no family history suggestive of a nutritional or intestinal disorder. During childhood and adolescence his growth and development were normal. He had had seasonal episodes of hay fever for 10 years, and had suffered from occasional attacks of bronchial asthma in the past year. In August, 1950, the patient noted the gradual onset of cramplike lower abdominal pain associated with four to six foul smelling, bulky, semiformed stools daily. During the fall of 1950, roentgenologic examination of the gastrointestinal tract revealed a distortion of the small bowel pattern "indicative of a nutritional disturbance." A barium enema and sigmoidoscopic examination were normal. He was placed on a bland diet and treated with vitamin B complex and oral liver extract; however, he continued to have abdominal cramps, diarrhea and weight loss without improvement.

In December, 1950, the patient was hospitalized and placed on a regimen consisting of a high protein, low fat diet and parenterally administered vitamins and liver extract. His stools were less bulky, but otherwise his symptoms were unchanged. One month later he had an episode of bright red rectal bleeding which necessitated rehospitalization. Except for the supplementation of five blood transfusions, there was no change in the therapeutic regimen. Repeated investigation of the gastrointestinal tract, including roentgenologic studies, sigmoidoscopy and examination of the stools for pathogenic bacteria, ova and parasites, revealed no obvious cause for his symptoms.

In February, 1951, the patient was admitted to the medical wards of the Mount Sinai Hospital because of the persistence and progression of his symptoms. His weight loss during the past seven months totaled 45 pounds.

Physical Examination: The patient appeared pallid, cachectic and chronically ill; his weight was 116½ pounds; the blood pressure, pulse rate and temperature were normal. The lower portion of the abdomen was distended; no masses were felt; no ascites was demonstrable. On rectal examination, no abnormal findings were noted. The remainder of the physical examination revealed no abnormalities.

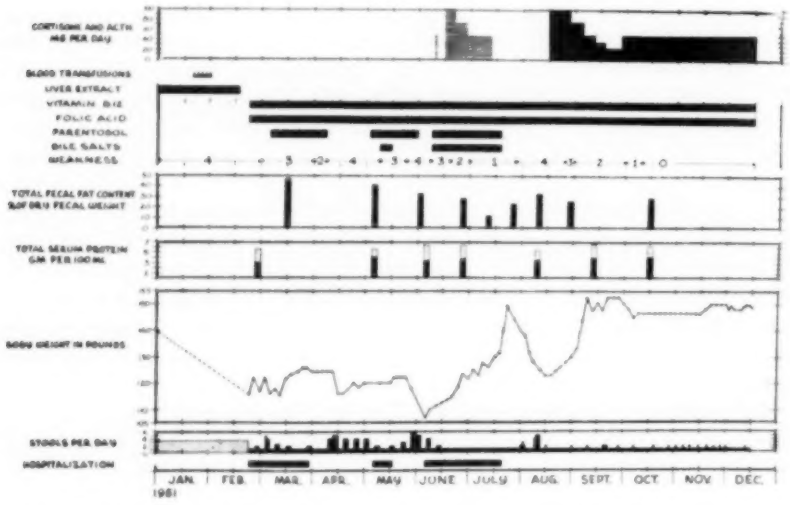

FIG. 1. The effect of cortisone and ACTH treatment in case 7, resistant to conventional sprue therapy (see case report). The lined areas indicate the dose and duration of ACTH therapy, while the black area indicates the dose and duration of cortisone treatment. The blocks representing total serum protein are divided into black and stippled areas, indicating the serum albumin and globulin fractions, respectively. The interrupted line of "body weight" and the stippled area in the "stools per day" columns are based on patient's history and indicate weight loss and diarrhea prior to hospitalization.

Three months of conventional sprue therapy failed to produce a clinical remission. After a course of ACTH there occurred a cessation of diarrhea, a dramatic increase in weight and a return of vigor. An exacerbation of symptoms followed soon after termination of ACTH therapy. With prolonged use of cortisone a clinical remission was again induced and has been maintained. The patient tolerates a normal diet satisfactorily and has returned to work after 10 months of inactivity.

Laboratory Data: The hemoglobin content of the blood was 11 gm.; the red blood count was 3,830,000 per cubic millimeter; there were 9,400 white blood cells per cubic millimeter, with a slight shift to the left; the platelets numbered 600,000. There was a mild macrocytosis present; the mean corpuscular volume was 96 cubic micra and the mean corpuscular hemoglobin was 29 micromicrograms. The prothrombin time was 18 seconds (control, 12.5 seconds). The bone marrow was very cellular and normal but for a slight increase in eosinophils. Repeated urinalyses were essentially normal. Stool examinations repeatedly revealed no ova or parasites and no pathogenic organisms on culture; there were occasional mildly positive guaiac reactions, large amounts of fatty acid crystals and occasionally an abundance of neutral fat. Three quantitative determinations of total fecal fat, expressed as percentage of dry

stool weight, ranged from 33.5 to 46.1 per cent. The fatty acid fraction varied from 23.9 to 28.4 per cent, and the neutral fat fraction ranged from 9.6 to 17.7 per cent. The erythrocyte sedimentation rate (Westergren) was 20 mm./hr. The blood urea nitrogen was 11 mg. per 100 ml.; the fasting blood sugar, 75 mg. per 100 ml.; the CO_2 combining power, 26 mEq. per 100 ml.; the serum chloride, 95 mEq. per 100 ml.; albumin, 3.0 gm. per 100 ml.; globulin, 2.7 gm. per 100 ml.; calcium, 9.2 mg. per 100 ml.; phosphorus, 2.0 mg. per 100 ml.; alkaline phosphatase, 12 King-Armstrong units; bilirubin, 0.2 mg. per 100 ml.; total cholesterol, 143 mg. per 100 ml.; esterified cholesterol, 106 mg. per 100 ml.; phospholipid, 189 mg. per 100 ml., and serum neutral fat, 430 mg. per 100 ml. The cephalin flocculation was negative and the thymol turbidity was 1 unit. The oral glucose tolerance test revealed a flat absorption

A B

FIG. 2. *A*. Photograph of case 7 (see case report) taken at the initiation of ACTH therapy in June 1951, after an unsuccessful trial with the accepted anti-anemic regimen. His weight at this time was 115½ lbs. This represents a loss of 64½ pounds from his highest weight.

B. The same patient in October 1951 after 77 days of continuous treatment with cortisone. His weight was 145 pounds. At this time the patient had a complete remission. He has now resumed normal activity.

curve; the figures at fasting, one-half hour, one hour, two hour and three hour intervals were 70, 75, 75, 85, 80 mg. per 100 ml. The intravenous glucose tolerance absorption curve, however, showed a normal pattern. Electrocardiogram was normal but for low T waves in the standard and the unipolar limb leads. Roentgen examination of the chest and skeleton was normal. Barium enema and sigmoidoscopy revealed no abnormalities. Examination of the gastrointestinal tract was reported as showing a normal esophagus, stomach and duodenum, but evidence of thickened mucosal folds, segmentation, flocculation of the barium column and dilatation of many loops of small bowel. The transit time was rapid; at the end of three hours the head of the barium column was in the rectum. An oral cholecystogram failed to outline the gallbladder. Pancreatic secretion studies (performed by Dr. Dreiling) before and after the administration of secretin revealed a normal flow of 4.2 c.c. per kilogram,

a normal bicarbonate concentration of 91 mEq. per liter, a normal amylase of 15.1 units per kilogram, and poor biliary flow suggestive of gallbladder dysfunction. The patient had a flat vitamin A absorption curve; the values at fasting, four hour, six hour and eight hour intervals were 31, 35, 31 and 28 micrograms per 100 ml., respectively. The fasting serum carotene was 58 micrograms per 100 ml.

Course: During the five weeks of hospitalization the patient was afebrile. After the diagnosis of primary sprue was established, he was placed on a high calorie, low fat diet and was given 20 mg. of folic acid per day and vitamin B supplement intramuscularly. He showed a rapid improvement, as evidenced by a 10 pound weight gain, disappearance of abdominal distention and cramps, and decrease in the number of stools to one to two per day. Because of inadequate hematic response, 10 micrograms of vitamin B_{12} were added daily and the dosage of folic acid was raised to 90 mg. per day shortly prior to discharge on March 31, 1951.

Following a dietary indiscretion, the patient noted the reappearance of one to four loose stools per day and occasional generalized abdominal pain. He was re-admitted on May 4, 1951, five weeks after discharge, with the onset of severe lower abdominal crampy pain, lasting approximately 10 minutes and recurring three to four times on the day prior to admission. The pain radiated to the right upper and lower quadrant and was not accompanied by nausea, vomiting, dysuria or diarrhea.

His temperature on this admission was 101.8° F. The only significant physical findings were voluntary abdominal spasm and mild direct tenderness to palpation in the right upper and lower quadrants. The laboratory findings were similar to those reported on his previous admission but for an elevated erythrocyte sedimentation rate of 71 mm./hr. (Westergren) and a prothrombin time of 43.5 seconds (control, 13 seconds). He had a mild leukocytosis, 10,450 white blood cells per cubic millimeter, but no shift to the left. It was not felt that the patient's symptoms required immediate surgical intervention; without specific therapy his temperature returned to normal and his abdominal symptoms disappeared in four days. Parenteral vitamin K corrected the hypoprothrombinemia within 24 hours. During the remainder of his hospital stay the patient was continued on a high calorie, low fat diet, vitamin B_{12}, vitamin K, folic acid and parenteral vitamin B complex. He was given a trial of bile salts, with no discernible effect. Upon discharge, on May 15, 1951, the patient weighed 120 pounds. During the next 10 days the patient's weight was maintained but he noted occasional episodes of abdominal cramps and two to three loose bowel movements per day.

Nine days before his third hospital admission, on June 4, 1951, he had an exacerbation of symptoms following a dietary indiscretion. He noted anorexia and a loss of 14 pounds; he had persistent watery, light colored stools (as many as six per day), and recurring mild abdominal pain and eructations. His weight on this admission was 107½ pounds. Physical examination revealed no additional significant findings. Repeated laboratory studies revealed no important changes except an elevation of the erythrocyte sedimentation rate and a mild hypoprothrombinemia of 19 seconds (control, 12 seconds).

It was felt that the antianemic and dietary regimen which the patient adhered to for three months failed to control his symptoms despite transient remissions. He was therefore given a course of ACTH therapy. A trial of 50 mg. of ACTH in 500 ml. of 5 per cent glucose in distilled water was given by continuous intravenous drip over an eight hour period for two days. Within 24 hours the patient felt subjectively stronger, appeared brighter, experienced a noticeable increase in appetite and had one dark, semiformed stool.

A four week course of ACTH, administered intramuscularly, was then given. The daily dose, divided into four equal parts, was 100 mg. during the first week, 75 mg. during the second week and 50 mg. during the third and fourth weeks. While the patient received ACTH therapy he was maintained on a high calorie, low fat

diet, restricting the sodium intake to 500 mg. per day. He was also given supplementary potassium chloride, and the previous antianemic therapy was continued.

During ACTH therapy the patient had a complete remission of symptoms and gained 18½ pounds, weighing 126 pounds at the end of the treatment period. His weight gain continued after cessation of therapy, reaching a maximum of 149 pounds after discharge from the hospital. His vigor returned and he became more active. He no longer had abdominal cramps and his bowel habits returned to normal for the first time in a year. The patient was clinically free of edema but for occasional observations of minimal pretibial swelling.

The oral glucose and vitamin A tolerance tests showed no change at the end of ACTH therapy. The most striking laboratory changes were an increase in the serum albumin from a pretreatment level of 3.1 gm. per 100 ml. to a post-treatment value of 4.3 gm. per 100 ml.; a fall in total fecal fat content from a pretreatment level of 33.5 per cent to a post-treatment level of 11.5 per cent of dry fecal weight (fatty acid, 6.75 per cent; neutral fat, 4.75 per cent). Moderate improvement of roentgenologic pattern of the small bowel was also noted.

The patient remained asymptomatic for about two weeks, when he again had an exacerbation of symptoms. He sustained a 27 pound weight loss in about two weeks, to 123 pounds, and noted anorexia and diarrhea, with as many as eight stools per day. Steatorrhea again became more marked; the total fecal fat was 32.5 per cent of dry fecal weight (fatty acid, 18.2 per cent; neutral fat, 14.3 per cent).

On August 15, 1951, the patient was placed on 100 mg. of oral cortisone daily. Again the patient noted a prompt remission of his symptoms. Over a period of five weeks his weight returned to 151 pounds, which he has maintained to the present writing (December 15, 1951). The important laboratory findings during the present course of therapy revealed an increase in the serum albumin from 3.2 gm. to 4.0 gm. per 100 ml., and an improved vitamin A tolerance test. The fasting, four, six and eight hour values of the latter were 22, 31, 50, 60 micrograms per 100 ml. serum, respectively; the fasting serum carotene remained unchanged. The oral glucose tolerance curve was again flat. In contrast to the findings during ACTH therapy, the fecal fat content has shown no significant improvement; two determinations revealed a total fecal fat content of 26.5 per cent on August 30 and 29.3 per cent on October 18. Roentgenographic examination of the small intestine revealed no change from the previous examination.

The patient has been receiving cortisone continuously for the past four months. The dosage has been gradually reduced to 50 mg. per day. His diet has been liberalized to allow for a normal consumption of fat and carbohydrates and a moderate sodium intake. The physical status of the patient has so improved that he has been able to return to work after an interval of 10 months.

The above case illustrates that ACTH and cortisone can induce a complete symptomatic remission in a patient with primary nontropical sprue resistant to conventional therapy.

Clinical improvement was accompanied by an elevation of serum albumin, a transient fall in the fecal fat content, and an improvement in the roentgenographic findings of the small intestine. Continuous administration of maintenance therapy proved necessary, since withdrawal resulted in an exacerbation of the disorder. Complete symptomatic remission was accompanied by a net weight gain of 43 pounds, normal bowel habits and a return to normal activity (figures 1 and 2). At the present time the patient satisfactorily tolerates a diet with no sodium restriction and with normal amounts of fat and carbohydrates.

Comments

Since Verzar and MacDougall's observation [5] of impaired glucose and fat absorption in adrenalectomized rats, the part played by the adrenal cortex in intestinal absorption has been extensively studied but not conclusively established.[6, 7, 8] As stated previously,[1] there is evidence to suggest that administration of cortisone or ACTH in patients with sprue affects intestinal fat absorption. The higher fasting serum vitamin A and carotene levels, the improved vitamin A tolerance tests and the lower fecal fat content observed in some patients indicate improved intestinal absorption of fat and fat soluble vitamins. Nevertheless, the effect of these hormones on appetite, sense of well being and mood may have contributed to the observed results of therapy and should not be overlooked.

It was hoped that cortisone and ACTH therapy, since it induced symptomatic improvement, might cause spontaneous remissions of the disease and thus allow discontinuation of hormonal administration. However, within one to five weeks after cessation of treatment, clinical relapses were noted despite the continuous administration of folic acid, vitamin B_{12} or liver extract.

Repeated courses of cortisone and ACTH resulted in the same improvement noted during the initial course of therapy. Clinical remissions and corrections of chemical changes recurred just as rapidly and on essentially the same dosage. No resistance to this form of therapy has thus far developed.

Because of the failure to maintain these patients in spontaneous remissions for any significant length of time after cessation of treatment, an attempt has been directed toward maintaining them on continuous therapy with minimal doses consistent with symptomatic remission. Maintenance doses have ranged mostly from 37.5 to 50 mg. of cortisone daily.

Cases 1 and 3, who have been receiving cortisone and ACTH therapy for 16 and 14 months, respectively, have now been given uninterrupted daily therapy for the past five months, while case 7 has been treated continuously for the past four months. With these small doses, no untoward reaction has thus far been observed and it has not been necessary to discontinue therapy. It is planned to alternate these prolonged courses of oral cortisone with shorter courses of adrenocorticotropin, given preferably in an absorption retarding vehicle.

The results of these observations indicate that the use of cortisone and ACTH does not constitute a cure for primary sprue. These drugs, however, cause a definite, often dramatic clinical improvement in patients resistant to the accepted forms of therapy. The improvement can be sustained by continuous administration of small doses of cortisone.

Summary

1. Eight patients with the sprue syndrome were treated with 13 courses of cortisone and/or eight courses of ACTH therapy. All but one patient

proved resistant to conventional sprue therapy prior to hormonal administration.

2. The administration of cortisone and ACTH does not represent curative therapy. However, a clinical remission was observed in all cases, the extent varying from patient to patient. Disappearance of the diarrhea, an increased sense of well being, improvement of appetite and gain in body weight, especially with prolonged treatment, were the important clinical manifestations. In some instances there was improvement of the serum albumin, the serum calcium, the roentgenologic findings in the small intestine and the content of fat in the stools.

3. Multiple courses of treatment with these hormones in the same patients resulted each time in clinical improvement, of essentially the same degree, in the same time interval, and on approximately the same dose. No instance of resistance to this form of therapy has thus far developed.

4. One to five weeks after cessation of hormonal therapy, clinical relapses invariably occurred. It was therefore found advisable to maintain therapy-resistant sprue patients on minimal doses of cortisone or ACTH compatible with the regression of their symptoms.

5. The practical management of sprue patients receiving cortisone and ACTH was outlined.

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SOME OBSERVATIONS ON POSTGRADUATE MEDICAL EDUCATION *

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A stimulating consequence of today's intensive laboratory and clinical investigation is the continuous unfolding of new ideas and more accurate concepts of the pathogenesis, the diagnosis and the treatment of diseases. There are two major avenues by which these new concepts may reach the practicing physician: (1) postgraduate education, and (2) current medical literature. The former is the more effective and desirable; the latter is becoming too voluminous to be sifted effectively by the individual. The medical profession's awareness of the increasing importance of postgraduate education is acute and universal.

After teaching a circuit-type postgraduate course in internal medicine in Oklahoma for the two years 1949–51, I have become aware of some of the problems relating to postgraduate education and have been left with thoughts which I hope may be of some value in this important phase of medical education.

In discussing any type of postgraduate education it would seem well to hold two things in view: 1. The outstanding purpose behind postgraduate education is to improve the quality of medical care. 2. The major factor in limitation of the breadth and scope of postgraduate education is the doctor himself, for with unlimited enthusiasm on the part of the doctor and a reasonable amount of time and energy available to him, it would be relatively simple to set up extensive and very effective programs of postgraduate education. In other words, postgraduate education generally will be about as effective and as successful as the physicians for whom it is intended want it to be.

There are two major types of sustained postgraduate training courses available today in many states, the *circuit* type and the *central* type. The *circuit* type is set up for the convenience of the doctors in the smaller and rural communities. The *central* type is usually set up in an academic center in a larger city. Generally speaking, the *circuit* type tends to be more "grass roots" with time and personnel factors necessitating emphasis on the practical; the *central* type is generally more academic and more detailed, but no less practical. Both types are needed, the one supplementing the other. Without the understanding of disease that attends the academic, the practical carries little meaning and is of little value. The best example of this latter, of course, is that most extensive program of postgraduate education that is being carried on in this country today, namely, that conducted by the detail men of our pharmaceutical houses.

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Circuit Type

The tremendous advantage of the *circuit* type of postgraduate teaching is its availability to the doctors throughout the state in the smaller communities. In general numbers, about 90 per cent of the physicians in a state will attend *circuit* type courses, as compared to about 10 per cent or less who will attend *central* type courses. It goes without saying that it is extremely difficult for many physicians in smaller communities to leave their practice for a week or even a few days to attend courses in a distant city. Regular vacation time, which should be spent in more restful diversion, is now spent by some doctors attending *central* type postgraduate courses.

There are two major types of *circuit* programs, with variations, being conducted in some states today:

1. A single instructor devotes his full time to teaching in small towns (and the large ones) throughout the state, taking about two years to cover the state. Oklahoma and Tennessee have had such programs for about 12 years, and The Commonwealth Fund of New York has been generously interested in this type of program as an experiment in postgraduate education. The state is divided into eight circuits, with five teaching centers in each circuit. In addition to the lecture held in the evening, bedside teaching can be done through three channels: (1) by private consultations whenever requested by the doctors in the class; (2) by teaching rounds in the community hospitals, and (3) by having doctors in the class bring diagnostic or therapeutic problem patients or interesting patients to an open clinic before the lecture. The instructor is in each teaching center one day a week for 10 weeks. With such a set-up there are 40 teaching centers in the state, and little driving is required of the physicians attending the courses. The disadvantages of this single-instructor type of circuit teaching are becoming more apparent. Two years is too long nowadays for one instructor to do the job well, since during that time new ideas, and especially new means and methods of treatment, will come along which must be evaluated and passed on to the group. Since during this time the instructor has been teaching exclusively, and seeing no patients of his own, his critical evaluation of a new antibiotic, or a new digitalis preparation, or new hormonal substances like ACTH and cortisone, must of necessity come entirely from the medical literature, which is frequently conflicting and not an entirely satisfactory source of teaching material. Also, with this type of program alone, courses will be available only once a week for 10 weeks, once every two years, which is not enough. Another disadvantage, experienced by those responsible for obtaining and appointing an instructor, is the difficulty in finding a good teacher who is willing to be a gypsy for two years, moving every 10 weeks or driving many miles from center to center. There are, however, *advantages* inherent in this type of program, an important one being that a large number of teaching centers can be established in a state, so a greater percentage of physicians can be reached by this type of course than by any

other type. Also, these courses have proved themselves at least in Tennessee and Oklahoma. The doctors like them and look forward to new courses each two years. The physicians who have had them are reluctant to give them up. Also, depending on the desires of the doctors, a great deal of time for personal instruction is available.

2. A second type of circuit teaching involves a group of instructors who go singly or as a group to rural community teaching centers, the instructors usually coming from medical school faculties. By necessity, fewer teaching centers are set up, and driving distances are greater for the attending doctors. Variations of this basic scheme are in operation in several states. It has been especially successful in Kansas. Programs are composed of afternoon hospital rounds, clinics and lectures, and one or more evening lectures the same day. Depending on how many teaching centers are set up, how many topics covered and how much driving the attending doctors are able or care to do, such programs can be made available to the rural communities one afternoon and evening every one to three months, and provide excellent year-round, stimulating, informative sessions. The *disadvantages* of this circuit-type teaching are few and rest largely on limitations imposed by availability of instructors on the school faculties, since the number of teaching centers will be roughly proportionate to the number of instructors available. In turn, the greater the number of teaching centers the higher the percentage of doctors who will attend. The *advantages* are numerous and center primarily on the desirable combination of providing bedside teaching by a diversified group of instructors, plus availability to a large percentage of physicians throughout the state. The programs can be extremely flexible and can be continuously presented the year round at frequent intervals, and teaching centers can be rotated to the satisfaction of all the doctors in the state.

Central Type

This type of teaching fulfills a need different from the circuit type in that the programs are generally more detailed, the subjects more thoroughly covered, and the appeal directed more to the specialties. A much smaller percentage of physicians will attend compared to the circuit-type courses. Along with the regular courses covering special fields for a period of a few days to several weeks, the residency type of central training lasting several months fulfills still another need and provides an excellent method of teaching, but is available to a still smaller number of men.

Some General Recommendations For Postgraduate Teaching

1. *Bedside Teaching:* It is my opinion that there is no substitute for good bedside teaching in medical education at any level. A glance at the evolution of teaching in our medical schools shows how the early emphasis on lectures has changed to direct contact of the student with the patient, and to teaching from the patient, not the podium. Unfortunately, it seems that postgraduate

teaching is having to experience about the same growing pains, since lecturing continues to constitute the most generally employed teaching method in most postgraduate courses. Patients still present more fertile material for discussion than the most pearl-enriched packet of lecture notes, and the patient is usually more stimulating. It is recommended that every effort be expended to conduct the major share of postgraduate teaching from the bedside, especially in the circuit-type course. Subtle points in history taking, physical diagnosis and interpretation of laboratory and x-ray findings can be brought out in a way which cannot be approached by lectures. Therapeutic problems can likewise be more specifically discussed.

2. *Content of Material Presented:* This should be no problem if the subject matter covered fulfills the three prerequisites so aptly put forth by Dr. Samuel Proger, of Tufts College Medical School in Boston, to wit: (1) It must be important, (2) it must be something the doctors want, and (3) it must be organized and presented in an easily digestible form. If any *one* of these three essentials is missing the material presented will fall short of its mark, no matter how well the other two requirements are met. In my own experience this simple formula has proved to be an excellent guide in selection of material for postgraduate teaching.

3. *Laying Groundwork for the Future:* Since a sharply limiting factor in the success and effectiveness of postgraduate teaching is the enthusiasm of the doctors themselves for the courses, I think it would be wise to establish concrete measures to make medical students aware of the necessity, advantages and pleasures of continuing their medical education after graduation. This would be especially applicable to state medical schools, the majority of whose graduates remain in that state to practice. A certain amount of enthusiasm and coöperation could be instilled in them during those formative years in school. It has become quite apparent to me that the degree of desire for postgraduate training is of the utmost importance. There is little doubt in my own mind that the physicians who made up a receptive enthusiastic group left the course as distinctly better physicians than those who made up a cool and refractory group. Looking ahead 10 years and more then, it would seem logical to think of postgraduate education also in terms of pregraduate education, to prepare good seeds as well as to care for the grown plant.

4. *Compulsory Postgraduate Education:* Unfortunately there are some physicians who will never voluntarily attend postgraduate courses. It would be highly desirable if the excellent example set by the American Academy of General Practice in establishing certain postgraduate education requirements could be applied to all practicing physicians. Not only should extensive measures be taken to provide all doctors with continuous and attractive postgraduate opportunities, but a certain minimal attendance every two or three years should be required. I believe it is the responsibility of the medical profession to see that men in the active practice of medicine

(regardless of their field) are not only adequately trained before entering practice but also continue to be adequately trained thereafter. A minimal requirement of about 20 hours of formal postgraduate training every three years is suggested.

5. *Abstract Service:* Keeping abreast of the medical literature nowadays can be a full-time job in itself. The busy family physician can be greatly helped in his daily practice by good monthly abstracts of current medical literature. Some journals, notably the *Journal of the American Medical Association,* supply this service to some extent. It would be of added help if the state medical journals carried a regular abstract section each month, say, abstracts of four articles of practical importance from each of the four major fields, Internal Medicine, Surgery, Obstetrics and Gynecology, and Pediatrics.

CASE REPORTS

ENDOCARDIAL FIBROELASTOSIS *

By C. Ralph Letteer, M.D., F.A.C.P., *San Antonio, Texas*

An unusual, puzzling and fatal type of heart disease in a 14 month old child was recently under observation on the pediatric service of the Robert B. Green Hospital. At the postmortem table, prior to examination, Dr. Louis J. Manhoff, pathologist to the hospital, after a brief perusal of the clinical data and on criteria to be elucidated later, expressed the opinion that the child had congenital endocardial fibroelastosis. This was confirmed by the pathologic examination. An informal survey among colleagues in medicine, pediatrics and pathology revealed that they, like the author, were not aware of the existence of knowledge concerning this entity. A somewhat cursory review of several of the standard textbooks in these fields revealed no discussion of this disease, though there was frequent mention of an endocardial abnormality in infants and children under the terminology of fetal endocarditis. The periodical literature contains several excellent articles which tend to delineate endocardial fibroelastosis as a distinct clinical and pathologic entity. Most of these appear in journals of pathology or clinical investigation and apparently have not come to the attention of clinicians generally.

It therefore seems worthwhile to report the observations on two additional cases and to review the literature concerning this disease.

Case Reports

Case 1. A Latin American girl, age six months, was admitted to the hospital February 16, 1951, with presenting symptoms of a cough and fever of two weeks' duration. She was said to have exhibited blueness of the lips for one week. Some time previously she had had difficult respiration, but a physician had reportedly found no abnormality. There had been some vomiting during the respiratory distress.

Examination revealed a fairly well developed and nourished child who was somewhat cyanotic and dyspneic. The dyspnea was diminished on placing the child in an oxygen tent. The heart sounds were faint, and some observers reported a systolic murmur at the apex. The liver was palpable but not markedly enlarged. There was no mention of adventitious sounds over the lungs.

An x-ray of the chest showed marked enlargement of the heart (figure 1).

The child died 27 hours after admission.

Postmortem examination showed a markedly enlarged heart weighing 97 gm. (The average normal weight at this age is 31 gm.[1]) The hypertrophy and dilatation were present in all chambers but were more prominent in the left ventricle. The myocardium was reddish brown and firm, and there were no foci of necrosis or fibrosis. The myocardium measured 8 mm. in thickness at the base of the left ventricle and 4 mm. in thickness at the base of the right ventricle. The endocardium of the left ventricle was greatly thickened and presented a smooth, glistening, opaque, grayish

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From the Cardiovascular Service of Robert B. Green Hospital, San Antonio, Texas.

white appearance (figure 2). There was no involvement of the endocardium of the other chambers or of the cardiac valves. The foramen ovale and ductus arteriosus had undergone normal closure. The coronary arteries were normal in origin, caliber and distribution.

Microscopic Description of Heart: Numerous microscopic sections of the heart showed an extensive uniform fibroelastic thickening of the endocardium of the left ventricle and left atrium. The endocardial thickening was composed of abundant elastic and collagen fibers, the elastic stain simulating the appearance of an elastic tissue stain of the aorta. There was no endocardial thickening of the other chambers and the valves showed normal histologic structure. There was marked hypertrophy of the myocardial fibers but there was no degeneration or fibrosis.

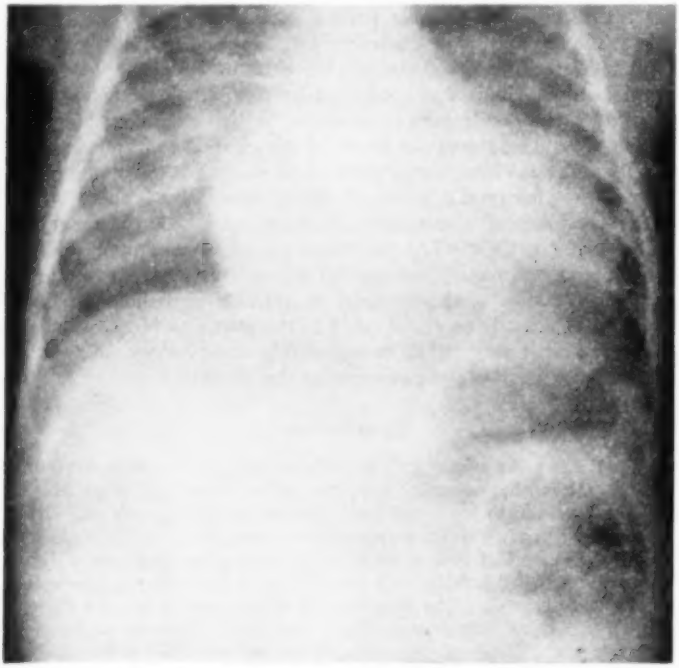

FIG. 1. *(Case 1)* Radiograph of the chest showing enlargement of the heart due to endocardial fibroelastosis.

There was marked congestion of the lungs with intra-alveolar extravasation of red cells, and there was moderate congestion of the spleen, liver and other visceral organs.

Case 2. A Negro girl, age 14 months, was admitted to the Robert B. Green Memorial Hospital on May 8, 1951, with a transfer diagnosis by a competent pediatrician of congenital heart disease. A chest x-ray had shown marked generalized cardiac enlargement. The possibility of pericardial effusion was considered, and two attempts at pericardicentesis had failed to obtain fluid.

The mother's gestation and parturition had been normal. The child had been healthy, as far as could be determined, until about four weeks prior to admission, when

she began to have paroxysms of coughing. She was also said to have had difficulty in breathing and swelling of the feet and face at times.

On admission the child appeared to be quite comfortable. A complete physical examination was negative except for the cardiovascular system. The pulse rate was 140. The point of maximal intensity was in the fifth interspace at the anterior axillary line. There was a Grade III systolic murmur at the apex. X-ray examination revealed marked cardiac enlargement (figure 3). Fluoroscopic examination and films in various projections failed to reveal alterations in the silhouette of the great vessels or of the chambers of the heart which could be interpreted as suggestive of any

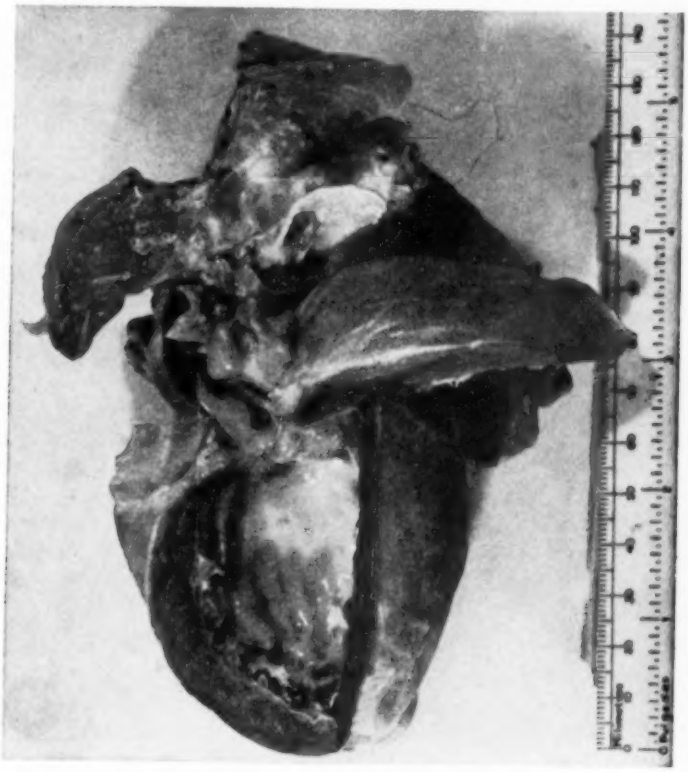

FIG. 2. *(Case 1)* Opened heart showing smooth, glistening, opaque, grayish white, thickened endocardium lining the left ventricle, and hypertrophy and dilatation of the left ventricle.

of the various congenital malformations. The electrocardiogram showed depression of ST in II, III, AVF and in V_2 through V_6 indicative of subendocardial injury and ischemia in the left ventricle (figure 4). The tentative diagnosis, therefore, was in no way securely established, but so-called idiopathic hypertrophy, anomalous origin of the left coronary artery from the pulmonary artery and von Gierke's disease were entertained as possibilities.

On May 14 the child developed respiratory distress and the paroxysmal coughing became more pronounced. A diagnosis of congestive heart failure was made. There was no substantial response to therapy, and the patient died quietly and somewhat unexpectedly on May 28.

At postmortem examination the heart was tremendously enlarged, weighing 172 gm. (The average normal weight at this age is 45 gm.) There was grayish white

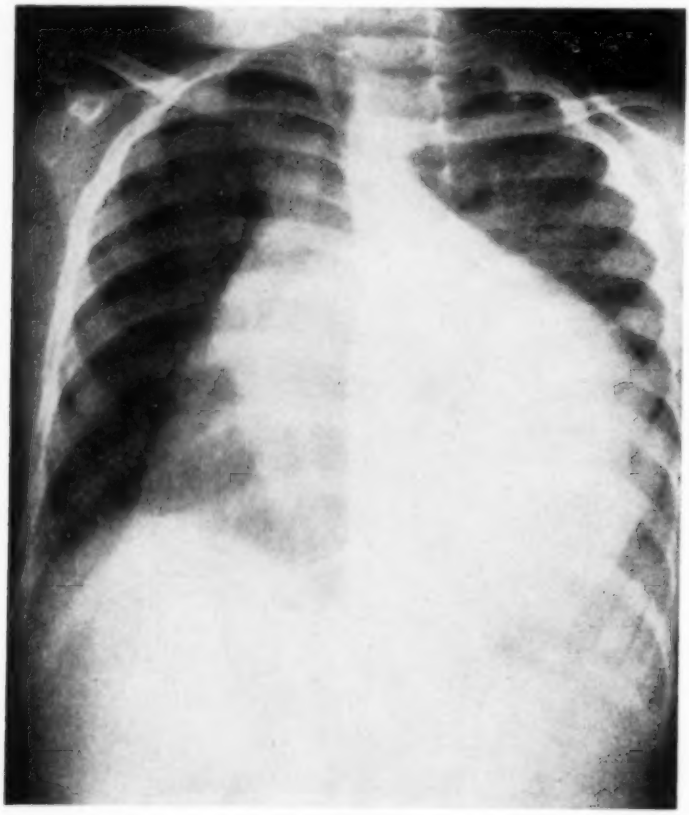

FIG. 3. (*Case 2*) Radiograph showing extreme enlargement of the heart. The patient is in an oblique position.

thickening of the endocardium of the left ventricle and there was questionable slight thickening of the endocardium of the left atrium, but there was no involvement of the valves or other chambers. On cut surface the thickened endocardium measured up to 0.5 mm. in thickness and produced a sharp white outline of the trabeculae carneae (figure 5). There was slight pallor of the subendocardial myocardium of the left ventricle. There were no abnormalities of the coronary arteries, septa or great vessels.

Microscopic Description of Heart: Sections of the left ventricle and left atrium showed a uniform fibroelastic thickening of the endocardium. The endocardium was sparsely cellular with abundant collagen fibers regularly oriented parallel to the ventricular surface. The elastic stains demonstrated numerous elastic fibers intermingled with the collagen fibers, comparable in amount to that in the aorta. Sections of the other two chambers and of all four of the cardiac valves did not show any appreciable thickening of the endocardium, consisting here only of a single layer of lining endothelial cells with but few delicate connective tissue fibers. The myocardium showed considerable hypertrophy of the muscle fibers but there was no degeneration, fibrosis or necrosis in the myocardium.

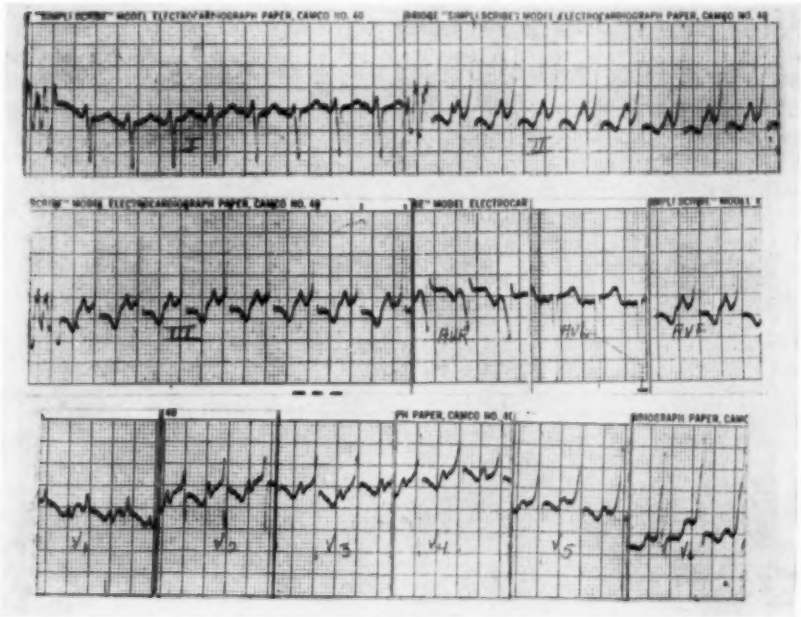

FIG. 4. (*Case 2*) Electrocardiogram showing marked right axis deviation in the limb leads. The electrical position is indeterminate. There are S-T and T abnormalities which are interpreted as evidence of ischemia of the subendocardial myocardium of the left ventricle.

There was moderate congestion of the lungs together with extensive focal atelectasis and a subacute bronchitis. No significant alterations were seen in the other organs.

HISTORICAL DATA

According to Rauchfuss, the concept of fetal endocarditis was introduced by Kreysig in 1816 as an etiologic and pathologic explanation for certain structural abnormalities, primarily stenosis or atresia of the semilunar valves observed in the hearts of infants.[2] Stohr credits Rokitansky, who was a contemporary of Kreysig, with introducing the term "fetal endocarditis" and with laying down rigid microscopic criteria for the establishment of this diagnosis.[3] During the

latter half of the last century fetal endocarditis was widely accepted as an entity and as an important cause of congenital cardiac abnormalities. In 1911 Fischer, again emphasizing the necessity of microscopic study, was able to accept only two of the cases reported up to that time as representing fetal endocarditis, because of the lack of histologic confirmation.[4] Pototschnig, in 1918, was the first to suggest that the changes described under this terminology consisted of a simple noninflammatory hyperplasia of fibroelastic tissue. Gross, in 1941, in a comprehensive review of the literature, analyzed the arguments for and against the inflammatory nature of the disease and concluded that the occurrence of fetal endocarditis had never been established, and that the valvular and parietal endocardial changes seen are better explained on the basis of a developmental defect.[5]

FIG. 5. (*Case 2*) Opened heart showing diffuse involvement of the endocardium of the left ventricle with endocardial fibroelastosis. The marked thickening of the endocardium is especially notable where the trabeculae carneae are sectioned transversely.

In more recent times the concept of fetal endocarditis has been supported by Abbott,[6] Farber and Hubbard [7] and Stohr [8] as late as 1934. It appears that virtually all the current standard textbooks devote a paragraph or more to so-called fetal endocarditis, and that most clinicians and pathologists adhere to the belief that it is a specific entity.

Since the article by Gross, there have appeared numerous articles devoted to pathologic material showing abnormalities of the mural or valvular and mural endocardium. The terminology of the titles has included fibrosis, sclerosis and, most recently, fibroelastosis, introduced by Weinberg and Himelfarb in 1943.[9]

These more recent authors, without exception, have accepted the postulate that the disease is due to a developmental defect of the endocardium.[9, 10, 11, 12]

There have also been several articles pertaining to idiopathic dilatation and hypertrophy of the heart in infants and young children.[13, 14, 15, 16] A review of these articles reveals that many if not all the hearts presented endocardial and myocardial changes, indistinguishable to the present author from the changes observed in endocardial fibroelastosis. These authors apparently were not cognizant of the significance of the thickening of the endocardium and, for the most part, directed their attention to the hypertrophy or to the degenerative changes in the myocardium.

In addition, there have been several articles pertaining to fibrosis or sclerosis of the endocardium occurring in young or older adults.[17-21] The various authors were apparently not cognizant of the occurrence of an at least somewhat similar endocardial disease in infants. One might speculate that these cases in adults may have been endocardial fibroelastosis in infants who survived to adulthood.

Levy and Rousselot [22] have described three cases of cardiac hypertrophy of unknown etiology in young adults. In each of these cases, mention was made that the endocardium was thickened, but this finding was not elaborated upon. None of the various known pathogenetic factors leading to hypertrophy was present in these patients.

Clinical Manifestations

The clinical manifestations and the course of the disease are quite constant and sufficiently typical to warrant a tentative antemortem diagnosis. Nearly all the patients have been children, varying in age from a few weeks to two years, though there have been instances in children as old as nine years. The patients have virtually always been regarded as normal by the parents and frequently by physicians until the onset of the symptoms of myocardial failure. This feature alone is of considerable value in ruling out the various types of congenital malformations. The onset is usually marked by the development of some form of respiratory distress, such as dyspnea or cough, often of a paroxysmal nature. A good number of the patients have been regarded initially as having a respiratory infection. Cyanosis has been observed in a large percentage of cases. Less specific symptoms, such as irritability, convulsions, edema, vomiting and anorexia, may occasionally be the presenting complaint. Within a period of hours, days or weeks, more striking evidence of myocardial failure presents itself and the child dies, often quite unexpectedly and without any dramatic event.

The physical signs are often not very striking. There may or may not be cyanosis, swelling of the face or dependent parts, enlargement of the liver, ascites or râles in the chest. The cardinal and indispensable feature is marked cardiac enlargement without alteration of the chamber or vessel silhouette, which might suggest some other specific type of congenital malformation of the septa, valves or great vessels. Murmurs, usually systolic at the apex, may or may not be audible and are in no way characteristic of the disease.

The diagnosis should be suspected in any infant or, possibly, in older children or adults when there is marked cardiac enlargement of a nonspecific type in the absence of the usual stigmata of other congenital heart disease, such as clubbing, polycythemia, persistent cyanosis or chest deformity.

Etiology

Numerous authors have postulated various etiologic factors, such as congenital syphilis, maternal influenza and maternal bronchitis. Many have considered rheumatic fever, either maternal or intrauterine, as responsible for the endocardial changes. Actually there is only one reasonably well authenticated case of rheumatic fever transmitted from a mother to the fetus.[23] It is significant that neither the clinical course nor postmortem morphologic abnormalities in this patient resembled the findings in endocardial fibroelastosis. Since the article by Gross, all subsequent authors have regarded the disease as a developmental defect. With the exception of Craig,[10] who made a detailed study of 37 cases, there has been little or no investigation along embryologic lines to prove that the endocardial thickening is a maldevelopment of the endocardium itself. It might well be postulated that maldevelopment of the coronary artery system, particularly the arterioluminal or arteriosinusoidal vessels, results in ischemia and subsequent thickening of the endocardium by a degenerative process. It should be pointed out, however, that the histologic character of the lesion is not suggestive of a degenerative process. It appears then, by a process of elimination, that maldevelopment of the endocardium itself is the most tenable explanation at the present time.

Pathogenesis

It is believed that the extreme hypertrophy and dilatation of the myocardium result from stasis and anoxia or ischemia occurring in the subendocardial myocardium. Gross, and also Cosgrove and Kaump,[9] called attention to the fact that the myocardial lesions in this disease often resemble healed bland infarcts. Flynn and Mann [24] state that it has been established that a narrow zone of the ventricular subendocardial myocardium is nourished from blood contained within the ventricular cavities themselves. It may be postulated that the thickened endocardium obliterates the orifices of the arteriosinusoidal and arterioluminal vessels, thereby preventing egress of arterial blood to this layer of the myocardium and producing ischemia. On the other hand, such obliteration of the vascular orifices may prevent ingress of blood from the coronary system to the ventricular cavity, thereby promoting stasis and anoxia in this region. Weinberg and Himelfarb [8] have supported this latter point of view. Prior and Wyatt [11] were impressed with the degenerative changes within the papillary muscles, and suggested that interference with their function was an additional factor in the production of ventricular hypertrophy.

Pathologic Anatomy

The essential gross pathologic alterations, namely, the cardiac enlargement and thickened endocardium, have been described in the above case reports. In many of the cases reported in the literature the endocardium of the valve cusps has been involved, producing valvular deformities. These valves have been described as thickened, nodular or slightly wrinkled, sometimes showing fusion of the leaflets producing stenosis. Surface vegetations have not been present.[12]

Cosgrove and Kaump have stated that if only the mural endocardium was involved the myocardial changes were scant, but if endocardial involvement was extensive and included the valves the myocardial involvement was more ex-

tensive. They imply that when the lesion is minimal and confined to the mural endocardium the valves may not be deformed, and that in the absence of valvular deformity myocardial involvement is less extensive. That this is not necessarily true is indicated by case 2, which shows very extensive involvement of the mural endocardium and a heart four times the normal weight, though there was no valvular deformity.

The present author believes that the degree of myocardial hypertrophy is proportionate to the degree of thickening of the mural endocardium. It is believed that the thickening of the endocardium occurs primarily in the left ventricle but that it may also involve other chambers or valves.

The microscopic pathologic findings have been described in detail and with excellent photomicrographs by Prior and Wyatt [11] and others.[9, 12] The characteristic changes are in the nature of a greatly increased amount of collagenous tissue arranged in layers parallel to the myocardium. Special stains have shown large numbers of elastic fibers within the collagenous matrix. The subendocardial-myocardial junction is often ill defined, and there may be finger-like projections of the endocardial layer into the myocardium. The myocardial fibers are hypertrophied, and hydropic degenerative changes may be present. Aschoff bodies have not been demonstrated in this disease, nor is there any cellular infiltration which could be interpreted as indicative of an inflammatory process.

Summary and Conclusions

1. The historical, clinical and pathologic data regarding an infrequently recognized but not uncommon disease of the endocardium are reviewed and two additional cases are presented.

2. It is believed that endocardial fibroelastosis is a distinct clinical and pathologic entity, and that it is the common denominator in cases which have been described under various terminology as congenital idiopathic hypertrophy, endocardial fibrosis, endocardial sclerosis and fetal endocarditis.

3. The diagnosis should always be suspected in the presence of otherwise unexplained marked cardiac enlargement in infants and children.

4. There is no factual evidence to support the concept of fetal endocarditis as an entity.

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LOCULATED AZYGOS FISSURE EFFUSION IN CARDIAC FAILURE*

By Robert L. Friedman, M.D., *Richmond, Virginia*

Interlobar effusions are not uncommon in cardiac failure. Most frequently they are loculated in the right lesser fissure, rarely in the azygos fissure. The rarity of this latter localization prompts the present report.

A point to be noted in considering the rarity of loculated effusion in the azygos fissure in cardiac failure is the incidence of the azygos fissure in routine chest surveys. In 50,000 examinations, Etter [1] found an incidence of 0.26 per cent; Litten,[2] 0.07 per cent in 8,000 cases; Minehart,[3] 0.13 per cent in 10,000 cases; and Pendley,[4] 1.05 per cent in 150,000 cases. Since the average incidence is probably below 1 per cent, the infrequency of loculation of effusion in the azygos fissure is more readily understandable.

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From the Department of Radiology, McGuire Veterans Hospital, Richmond, Virginia.
Sponsored by the Veterans Administration with the approval of the Chief Medical Director. Statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Stein and Schwedel [6] and Stivelman [7] each reported a case of loculated azygos fissure effusion; the following is believed to be the third case recorded.

Case Report

A 69 year old male had been admitted to the hospital on two separate occasions complaining of increasing shortness of breath and general weakness. On the second admission, the patient was found to have a large right pleural effusion. After thoracentesis the lung failed to reëxpand. A decortication was attempted but had to be abandoned because of the poor condition of the patient. He was discharged four weeks postoperatively with a diagnosis of arteriosclerotic heart disease with chronic cardiac insufficiency.

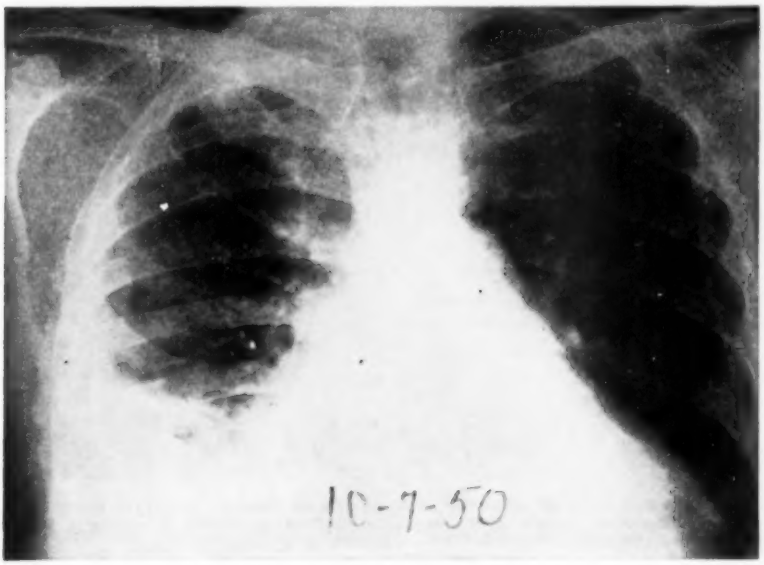

Fig. 1. Chest x-ray on the previous hospitalization demonstrates haziness of the right lower lung field, probably due to thickened pleura. An incidental finding is the presence of an azygos fissure.

After discharge, dyspnea and weakness progressed rapidly. He developed a cough productive of a small amount of sputum and noted that his legs and abdomen had become markedly swollen. He was therefore admitted for the third time.

Physical examination revealed dullness to percussion over the lower half of the right lung field; breath sounds were diminished to absent over this area. Crackling râles were heard over both bases posteriorly. The heart was enlarged to percussion. Heart sounds were distant. A systolic murmur was heard at the apex. The cardiac rhythm was irregular, apparently due to extrasystoles.

The abdomen was enlarged and fluid was present. There was tenderness to palpation over the liver area. The extremities revealed 4 plus pitting edema.

Laboratory studies were within normal limits except for a 3 plus albuminuria.

Venous pressure was 28.0 cm. of saline. The circulation time, arm-to-lung, with ether was seven seconds, and the arm-to-tongue with Decholin was 25 seconds.

Chest x-ray on the previous admission (figure 1) demonstrated haziness of the right lower lung field, probably due to thickened pleura, a sequel of the previous surgery. The heart was moderately enlarged. An incidental finding was the presence of an azygos fissure. Examination of the chest on the current admission (figure 2) revealed a fusiform homogeneous density in the region of the azygos fissure, but the fissure was not visualized. The roentgen findings suggested a loculated azygos fissure effusion.

After a period of bed-rest, digitalization and mercuhydrin therapy, the patient showed marked clinical improvement. Follow-up x-ray of the chest (figure 3)

FIG. 2. Chest x-ray on admission demonstrates the findings unchanged except for the fusiform homogeneous density in the region of the azygos fissure, indicating a loculated azygos fissure effusion.

demonstrated the disappearance of the fusiform density previously described and the re-appearance of the azygos fissure as noted on the previous admission.

Subsequently, the loculated azygos fissure effusion re-accumulated. The patient's condition deteriorated and death occurred several weeks later. Autopsy permission was not granted.

COMMENT

In his recent report of interlobar hydrothorax in cardiac failure, Robertson [5] noted only 36 reported cases. From an analysis of these cases, it was noted that the majority occurred in the right lesser interlobar fissure (24 out of 29 cases). He also registered data showing that 23 of 28 cases were 40 years of age, and in 14 of 36 cases there was no accompanying effusion in the general pleural cavities. Necropsy study in five cases showed fibrous obliteration of the general pleural cavity.

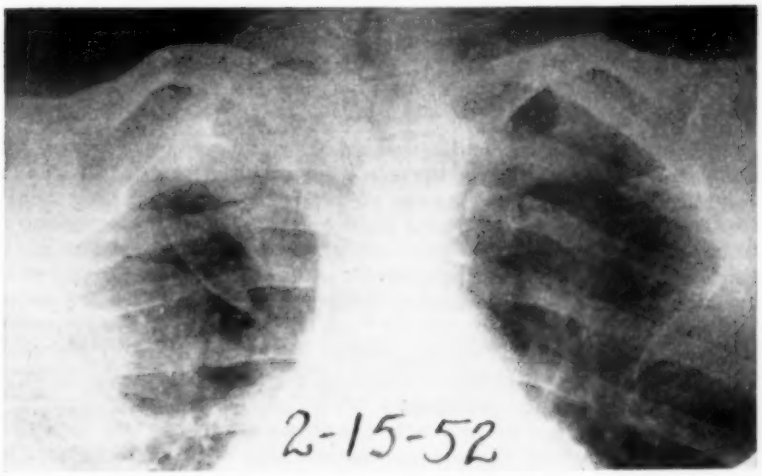

FIG. 3. Restudy of the chest after therapy for the cardiac failure reveals the absorption of the azygos effusion and the re-appearance of the azygos fissure.

The present case coincides with these findings, as the patient was over 40 years of age, and there was no accompanying generalized effusion. It is very likely that the pleural space had been obliterated by fibrous adhesions as a result of the previous hydrothorax and the surgical procedure that followed for decortication of the lung.

SUMMARY

A case of loculated effusion in the azygos fissure in cardiac failure is reported, and a review of the pertinent literature is presented.

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MEDICAL THYROID STORM: A PSYCHOSOMATIC STUDY *

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THERE are few more dramatic or challenging medical emergencies than thyroid storm. Its sudden development in the nonsurgical thyrotoxic patient is rightfully regarded as an ominous sign, and all therapeutic efforts are overshadowed by the knowledge that the outcome is usually fatal. Little is known about this emotional and endocrine tempest, and opportunities for observing it in medical patients are rare. Among 2,033 thyrotoxic patients seen over a 25 year period at the Massachusetts General Hospital, McArthur [1] reported 11 medical patients with storm, eight of whom died. Bayley [2] and Lahey [3] report similar figures.

The psychodynamics and physiopathology of this condition are not clearly established despite many excellent studies of the predisposing conditions,[4, 5, 6] precipitating stresses,[2, 3, 4, 7] pathogenesis [8, 9, 10, 11, 12] and autopsy findings.[13, 14, 15] The influence of strong emotional factors in thyrotoxicosis has long been recognized,[16, 17] and in the past 30 years psychiatric studies [18–24] have contributed materially to our understanding of the personalities of patients who develop thyrotoxicosis. More recently Lidz and Whitehorn [25, 26, 27] and Ham, Alexander and Carmichael [28, 29] have suggested psychodynamic formulations which may significantly alter the traditional treatment and management of these patients. No report has been found in the literature discussing thyroid storm from the viewpoint of the patient's personality and the emotional stresses which precipitated the crisis. The following patient's history is considered interesting in this respect.

CASE REPORT

S. T., a 73 year old white widow, was admitted to the Mary Hitchcock Memorial Hospital on June 21, 1950, complaining of vomiting of one week's duration, anorexia, alternating constipation and diarrhea for six weeks, and weight loss of 25 pounds in the preceding four months. At that time she had developed an illness characterized by fever, malaise, nasal obstruction and a productive cough, considered by the family to be "the flu." This condition gradually subsided but left her weak, depressed, increasingly anorexic and suffering from bouts of alternating constipation and diarrhea. Her persistent deterioration prompted the family to consult a physician, in spite of long-standing distrust of the medical profession. The family doctor noted that the earlier respiratory infection had subsided, and he felt that in time her condition would improve. Persistence of her symptoms, augmented by vomiting, diarrhea, increased irritability and agitation, compelled him to obtain hospitalization against her wishes.

Past history revealed that she had enjoyed good health and, apart from a hysterectomy at the age of 50 for menorrhagia, had had no serious illnesses. She rarely consulted a physician, although her family remarked that she usually exaggerated the seriousness of any illness or stressful situation.

The patient was the fourth of five children, the daughter of a prosperous dairy

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farmer who was described as passive, mild mannered and kind. The mother was demonstrative, affectionate and warm-hearted. "My mother was a saint. She brought me close to God and, in fact, the first words I uttered were a prayer." The mother was the dominant figure in the family, and the patient speaks of being particularly attached to her. "I was more interested in religion than the other children, and mother and I were very close. I loved my father but he did not have the same interest in religion." Excessive neatness characterized the mother's behavior. Tidiness, cleanliness and fastidiousness were emphasized as cardinal virtues. The expression of hostile feelings toward anyone was virtually impossible, and the patient adopted attitudes of good will toward all. She was excessively orderly, washed her hands frequently and was readily embarrassed by reference to bowel function. She scrupulously tried to prevent unpleasant body odors, and before having a bowel movement took every precaution to see that no one else was planning to use the bathroom immediately after her.

The patient grew up on a large farm where there was usually ample help and the opportunity for a leisurely existence (see figure 1). She attended school until 13, completing the eighth grade, but, rather than go to high school, preferred to remain about the home, spending much of her time with the farm animals. There were a few

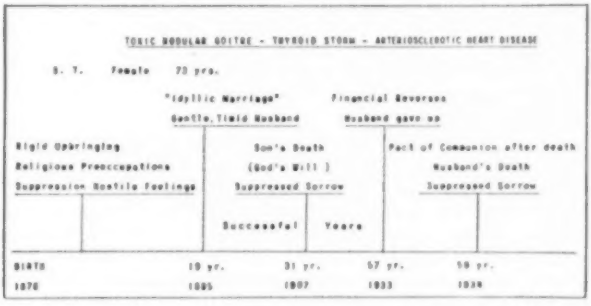

FIG. 1. Schematic representation of patient's life history from birth to age 58.

friends whom she usually met through her participation in church affairs. The whole family tended to be rigidly puritanical, and all abstained from smoking, drinking and swearing. At 13 she joined other members of the family in the church choir. "I had a beautiful voice and God meant me to sing in His Church. At first I was hesitant but something seemed to urge me forward. When I finished singing my first solo, there was not a dry eye in the church."

At 19 she married her childhood sweetheart, a kind, gentle, rather timid person four years her senior. "The idea of marriage had never occurred to me. At first I balked, but my mother said 'He needs you, darling, to look after him.'" The patient described her marriage as "idyllic." "There was never a cross word. . . . He worshipped me. He was a saint, like mother, but he was weak and his health was poor." She cared for her husband like a child, and derived deep satisfaction from the knowledge that she was necessary to someone.

The husband achieved temporary prosperity as the owner of a large dairy farm and there was always domestic help to assist the patient. She was an enthusiastic hostess and, according to her daughter, "thought nothing of entertaining as many as 20 people at a time without notice." There were four children, but the eldest died at 12 of "Bright's disease." The loss of this boy's love was a severe blow, but she stifled her feelings at the time and showed little reaction on the surface. "He was a

saintly boy, he was too good to live and we were resigned to God's will." In 1933 further disaster overtook the family. In one year their herd of cows had to be destroyed and two horses were lost. Accumulated debts forced the sale of the family farm. The patient and her husband then lived with their eldest daughter (M. M.). Such was the impact of losing the farm that the patient could not bring herself to drive past it for many years. Following this catastrophe "my husband gave up. 'There is a better home for me,' he said, and the next year he died." Again she restrained all evidence of her sorrow and refused to cry. "I kept it all inside me. Before his death we made a pact that we would always be true and that after death we would try to commune with each other. God was good to us and soon after his death I saw my immortal husband's body in the glorious heavenly light. In my agony I heard his voice saying, 'The peace of God passeth all understanding.' He stood there and then I retired to Earth." The patient described this incident with great religious fervor on several occasions, during which she was carried into a brief, trancelike state. Since this ecstatic event she had "communicated" with her husband in thought many times, and every night for 17 years she had prayed for sudden death. "I wanted to join him more than anything else in the world."

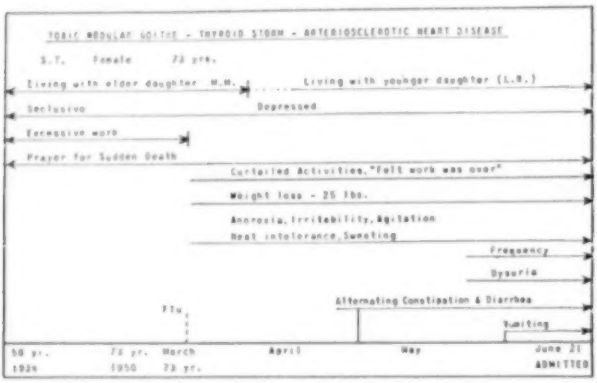

FIG. 2. Schematic representation of patient's life history from age 58 to hospital admission.

The patient was left enough money by her husband to protect her against financial want. Both daughters emphasized to her that she was always welcome in their homes, but she chose to continue living with M. M., who was her "favorite" daughter. The patient never really adjusted to the loss of her husband, and gradual personality changes were noticed by all three of her children. She could never discuss his death or what it meant to her. She found it difficult to sleep at night and wrote poetry expressing her pent-up feelings. She stopped singing in the church, became more seclusive and lost track of her friends, and her religious preoccupations increased. "The religion mother gave me has been my whole life."

During the 17 years preceding her hospitalization (see figure 2), she gradually demanded more affection and recognition in the home and encouraged these by excessively hard domestic work, often doing unnecessary manual tasks with exceptional attention to orderliness and cleanliness. Her daughter pleaded with her to do less but the patient continued. She said, "My daughter was working herself to death caring for a large home, and I was killing myself trying to save her. I couldn't watch anyone else killing herself without going in and doing it too." She was asked what her

daughter's gratitude meant to her. "Oh, it meant everything. She did not show her affection much but I could not have gone on without it."

The daughter M. M., a practical nurse, was a large, obese, forthright individual who drove herself to maintain her rigidly fastidious standards about the home. She emphasized her great affection for her mother at some length, but further evidence suggested that she had other feelings. In an unguarded moment the patient described her daughter as "hard." In due course it was established by the children that M. M. and her husband were to care for the patient and, in return, would receive her estate. The burden of care became heavier than the daughter had anticipated, and she expressed increasing annoyance at her mother's constant activity and interference about the kitchen. She believed in later years that many of her mother's troubles were "mental," and at one time considered having her seen by a psychiatrist.

In March, 1950, four months prior to admission, M. M. decided to take definite action. She told her mother that she could no longer work about the house, that she must restrict her activities to sewing and minor sedentary pursuits. The patient said, "I felt then that my work was over, that I was no longer needed, and that He would take me. I felt that I was now nearing the end of my long climb up the ladder to Heaven and my loved ones." Shortly after this she developed "the flu." She refused to see a physician and remained in her room after the acute phase of the illness, depressed and uncooperative. Relations between the patient and M. M. became so strained that the latter requested her sister (L. R.) to take the patient for a time. In addition to this act of rejection of the patient, there were strong feelings of hostility between the sisters, and L. R. remarked that M. M. "just dumped mother on me." At the time, the patient was greatly distressed at having to leave M. M.'s home, but later she interpreted the change as part of a family campaign to get her medical attention. At L. R.'s house her behavior remained unchanged. She was convinced that she was going to die, felt guilty at being a burden to her family, and prayed more fervently than ever for sudden death. It was at this point that a physician was called. "He said I had recovered from 'the flu' but I knew I was sick with other thoughts and feelings. I prayed to die; that has been in my head for years." Her physician felt her persistent downward course was due to arteriosclerotic heart disease and gastrointestinal malignancy, and sent her to the hospital.

System review brought out the following facts. She had had intermittent sinusitis for many years, with a postnasal drip and frontal headaches. She had experienced increasing exertional dyspnea in the past year, and recently had noted ankle edema in the evenings. At times she felt her heart beating irregularly: "It keeps stewing, but it won't kill me." She had taken digitalis until a week prior to admission. For many years she had had varicose veins in the left leg, and two years prior to admission had had a superficial thrombophlebitis in the left leg treated by a physician. There had been increasing heat intolerance in the past few years and marked sweating and weakness recently. She denied emotional lability, but her family believed such behavior was characteristic. She complained of dysuria and frequency in recent weeks. Her relatives were aware of increased prominence of her eyes in the three months prior to admission.

The patient was a slight, agitated, dehydrated woman with obvious exophthalmos, moderate flush and a fine digital tremor. She had lost weight and appeared chronically ill, but was in no immediate distress and cooperated perfunctorily with her physicians. Basically, she was negativistic and rejecting in her attitudes. Her temperature was 98°F.; pulse, 99; respirations, 20; blood pressure, 180/68 mm. of Hg, and weight, 124 pounds. The skin was smooth and warm. There were bilateral lid lag and poor convergence; cataracts obscured the fundi.

The thyroid was palpable, with a firm 2 cm. nodule in each lobe; there was no bruit. The lungs were clear to percussion and auscultation. The heart extended 12

cm. to the left of the midsternal line in the fifth interspace. The rhythm was totally irregular, and there was a Grade II blowing systolic murmur, loudest at the apex. The abdomen was protuberant, with generalized guarding and more marked resistance in the epigastrium. There was a well healed midline suprapubic scar; no organs or masses were palpable. Pelvic examination disclosed a normal cervical stump; early leukoplakia was present about the vulva and perineum. Rectal examination was normal. There were 2 plus pretibial edema and moderate bilateral varicose veins. There were slight increase in the deep tendon reflexes on the right and minimal impairment of vibration sense in both legs.

Laboratory studies showed a hemoglobin of 10.4 gm. (Klett photometer), red blood count of 3,940,000, white blood count of 4,800 with normal differential, and a negative serologic reaction by the Mazzini method. A voided urine specimen was amber in color, cloudy and acid in reaction. The specific gravity was 1.019; sugar and bile tests were negative. There were .02 gm. per cent albumin and 15 white blood

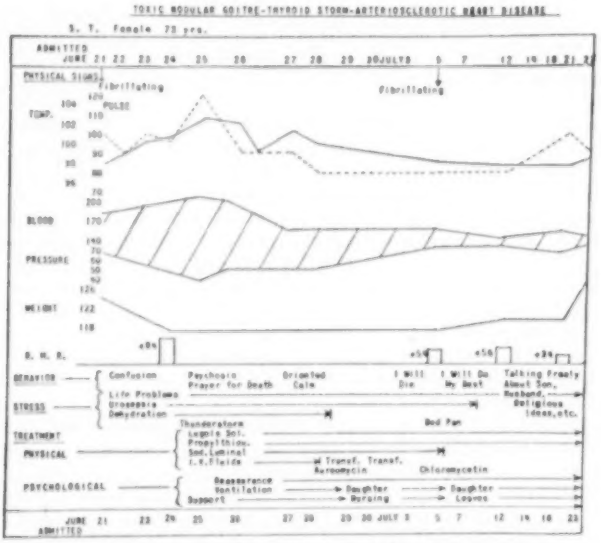

FIG. 3. Schematic representation of hospital course.

cells/10 high power fields, and rare bacteria. A blood cholesterol was 187 mg. per cent; a blood urea nitrogen was 22 mg. per cent. The total serum proteins were 5.5 gm. per cent, the albumin, 3.8 gm. per cent, and the globulin, 1.7 gm. per cent. Three stool examinations showed no occult blood. Chest x-ray and cardiac fluoroscopy showed "slight cardiac enlargement with prominence of the left ventricle; torsion and calcification of the aortic arch; lung fields clear except for slight fibrosis in the right cardiophrenic angle." The initial electrocardiogram showed regular sinus rhythm and digitalis effect.

The admission diagnoses were: toxic nodular goiter, hypertensive and arteriosclerotic heart disease with auricular fibrillation and borderline decompensation, malnutrition, bilateral cataracts and varicose veins. It was considered important to exclude a gastrointestinal malignancy.

During the evening of her second hospital day (see figure 3) she became mildly

confused and during the night fell out of bed. Her confusion was greater the following day and her temperature rose to 100.8°F. (oral) and her pulse to 100. A second neurologic examination showed no change. Toward the end of the third day she seemed clearer and, although restless, slept well. Two successive basal metabolic readings done on the fourth day were plus 94 and plus 100, but the tests were considered unsatisfactory because she vomited several times, had fever, and was reported to be quite "nervous." Her pulse was 96 during the tests. On this day she was moved from the open ward to a private room. She again developed fever, which reached 101.6°F. and persisted all night at this level. The morning of the fifth day, excitement and confusion were marked. She was flushed, perspiring profusely and hyperpneic, and the pulse was 120 with regular rhythm. There was an exacerbation of her anorexia, vomiting and diarrhea. The onset of these symptoms coincided with the development of a loud thunderstorm. This was evidently of great significance to her, and she later recalled an incident in childhood, her first personal religious experience. She was standing under a tree terrified by a fierce storm. "I prayed to God to take away my fear, and as if by a miracle, my fear disappeared." Now another great storm prompted her to pray for another miracle. She prayed again for sudden death and was certain that her prayer would be answered.

Physical examination at this time was essentially unchanged. There was no alteration of the blood count, and a blood culture was subsequently reported as sterile. She complained of dysuria and frequency; a urine specimen showed 200 white blood cells/10 high power fields and was loaded with bacteria. A pure culture of coliform organisms was reported subsequently. She was dehydrated and probably had lost substantial amounts of electrolytes in her diarrhea, vomitus and perspiration. An infusion of 1,000 c.c. of 5 per cent dextrose in normal saline produced no significant change.

In the evening she was worse. Her temperature had risen to 102.8°F. (rectal), her pulse was full and collapsing, the rate was 110 with frequent ectopic beats, and her blood pressure was 204/40–0 mm. of Hg. Excitation, disorientation with paranoid ideas, hyperactivity, flush, perspiration, diarrhea, vomiting, exophthalmos and stare were striking. A diagnosis of acute medical thyroid storm was made and treatment was instituted.

Initial measures consisted of Lugol's solution, 0.6 c.c. in 200 c.c. of 5 per cent dextrose in water, 20 c.c. of 50 per cent dextrose, 3 c.c. of Parentosol (Squibb), all intravenously, Sodium Luminal, 0.12 gm. subcutaneously, propylthiouracil, 300 mg. by mouth, adequate additional intravenous fluids, and sponge baths to reduce the fever. The intravenous Lugol's solution in 5 per cent dextrose and water was repeated every six hours for two days. There were frequent extended visits by her physicians, and after several interviews a general formulation of the psychodynamics of the situation was possible. During the height of the thyroid storm, psychotherapy consisted of discussion of her thoughts and feelings and of strong reassurance. The response to treatment was dramatic. In 12 hours her temperature had fallen to 99.4° F. (rectal) and her pulse to 80. She was calmer, her disorientation had cleared and she was improved in every way except for the gastrointestinal and urinary symptoms.

The morning of the sixth hospital day she was further improved clinically. An electrocardiogram showed auricular fibrillation which had been present transiently on other occasions. Aureomycin, 250 mg. four times a day, was given empirically to control the urinary infection, pending receipt of antibiotic sensitivity reports. Nausea and vomiting persisted, but under the strong suggestion and encouragement of her physicians she was soon able to take fluids and, in several days, a soft diet. On the eighth and tenth hospital days small transfusions of citrated blood, each 250 c.c., were given to counteract the anemia. By this time the pretibial edema previously noted had disappeared.

Her daughter (M. M.) was now allowed to nurse her for 12 hours a day. This gesture pleased her, and she stated that she was grateful for affection and attention from a member of her own family. Confirmatory information about her personality and background was obtained from the daughters M. M. and L. R. and from a social service investigation. Psychotherapy on a necessarily superficial basis was continued. It was suggested that God might not have meant her to die at this time, that possibly she had been wrong in praying for death for so many years, and that if God had meant her to die He would not have brought her to the hospital. Such an approach appealed to her strong religious beliefs, dealt directly with the psychologic forces which had precipitated the thyroid storm, and allowed her to "save face." This gave her a basis for new hope without requiring any drastic reorientation of her attitudes or behavior. She grasped at these straws readily and in a day or two was able to say, "Now I pray for forgiveness; I pray for life." There was a steady improvement in her condition, as shown by her attitudes, appetite and vital signs, until the fourteenth day, when the patient was observed to be more excited and confused. Slow auricular fibrillation was present. Her blood pressure was 136/56 mm. of Hg. and her weight, which had increased to 126 pounds, showed a loss of four pounds. She was extremely negativistic and destructive in her attitudes at this time, and told her daughter, "Even though they've pulled me out this time, I'm going to be an invalid anyway—and I will die." She recognized the relation between her irregular pulse and emotional state. She said that during the previous night, while waiting for the bedpan, she had been upset by fear of wetting the bed, "then that pounding and irregular beating began again, just as it had been for so long before I came to the hospital." Further discussion of her thoughts and feelings was encouraged and reassurance was given in large measures. Propylthiouracil was increased to 400 mg. a day and Lugol's solution maintained at 0.6 c.c. four times a day. Chloromycetin, 250 mg. four times a day, was given to control the urinary infection, which had been reported sensitive to this antibiotic, and all urinary symptoms subsided in several days.

From time to time the patient relapsed briefly to her earlier ways of thinking, but gradually she realized that she was going to live and so took a new interest in life. She felt at first that she must try to live for the sake of her physicians. "I want to do my best. You have all given so much and I cannot let you down. I realize that it was a sin to want to die." Later on she said, "I have a new lease on life and I am going to keep on as long as there is work to do."

On the sixteenth hospital day the basal metabolic rate was plus 52 and plus 54 on two successive tests. An electrocardiogram showed a sinus tachycardia and first degree A/V block. Gradual ambulation was started. Her gastrointestinal symptoms had almost entirely subsided. On the eighteenth day M. M. left to return to her own home and the following day the patient remarked, "Yesterday I had the best day I've ever had."

A reduction in the doses of Lugol's solution and propylthiouracil was attempted, but there was increased evidence of toxicity, and the latter drug was given in divided doses of 100 mg. four times a day and Lugol's solution was given 0.6 c.c. three times a day. The latter was continued until the twenty-eighth hospital day.

By this time she had come to talk more freely of her life and problems and it was felt that, although her underlying personality had in no way been modified, some of her attitudes and drives which were so destructive had been redirected. All symptoms present on admission had disappeared, her weight had increased to 130 pounds and her temperature and blood pressure were stable. She continued to have occasional bouts of sinus tachycardia. Her basal metabolic rate was now plus 34 and her urine was normal. The day prior to discharge she volunteered, "I shall take a different view from now on with better motives. I shall not pray for sudden death; I went pretty low. I shall try to live if I can only be of a little service to someone." She

was discharged to her family physician on the thirty-third day on propylthiouracil, 100 mg. four times a day. It was felt that surgery was contraindicated at this time.

Follow-up letters six months after discharge stated that she was progressing well, although her behavior and attitudes were essentially unchanged.

Practical considerations made follow-up at this hospital impossible.

Discussion

By definition, a psychosomatic disease is one manifested by interrelated psychologic and physiologic disturbances. Effective therapy may often have to be applied at various levels simultaneously, particularly when the patient is seriously ill and death is a possibility, as in the present case. Unfortunately, there is no complete understanding of the thyroid storm to help in planning treatment, but from the evidence in the literature and the observations of our patient it is possible to attempt a formulation.

Undoubtedly multiple factors participate in the development of the hyperthyroid state, and in a given patient one or more elements may predominate. Ultimate understanding requires a broad viewpoint and careful evaluation of the continuum which links emotional factors on the one hand with organic pathology on the other. Hereditary factors are suggested by the frequent finding of a familial history of goiter, and the careful work of Martin and Fisher [5] indicates that a single recessive gene favorable to the development of primary thyrotoxicosis is present in these patients. Warthin [6] has emphasized the gross and microscopic constitution of thyrotoxic patients and the "thymico-lymphatic diathesis" as a background for the development of the disease under suitable stimulus. Our patient had had "the flu" in March and had a urinary infection, which undoubtedly played a rôle in her total response. Cohen [13] has noted the rôle of infection in precipitating thyroid storm. In the patient described above, malnutrition and weight loss were also present. These factors, however, seemed to be of considerably less importance than the psychological forces.

Lidz and Whitehorn's studies [25, 26, 27] have shown fairly conclusively that women who develop hyperthyroidism have felt rejected as children by their mothers in favor of other siblings and seek to restore their positions by becoming the "good children" who identify with their mothers. The latter are usually strict, rigid, self-sacrificing individuals, and the fathers are relatively weak and ineffectual. In the present patient these relationships were observed. The patient identified with the mother. Goodness and approval became her prime objectives in life. The expression of hostile feelings was forbidden. The father, we are told, was weak and passive and, as with Lidz' patients, our patient chose a husband in the image of her father. The husband lavished attention on her, and in caring for him she felt secure. After his death the children became the foci of her attention and she perpetuated her mother's teachings that children must care for their parents. She lived with her daughter and found her great needs for affection and approval gratified by the attentions which she solicited so urgently from her daughter. She seemed plagued by the fear that she might lose this affection. These again are part of the patterns observed by Lidz,[27] who has found the fundamental precipitating factor in the disease to be the "disruption or threat of disruption of the dominant interpersonal relationship upon which [the patient's] security rests." Our patient was threatened with just this situation

when her daughter told her to stop her intense domestic activity. This was a simple, well intentioned demand, but it proved an almost catastrophic rejection for the patient, who interpreted it as a loss of approval and of life satisfactions which her work brought her. "I felt then that my work was over; that I was no longer needed, and that He would take me." As Ham and Alexander [28, 29] emphasized, these patients are basically frightened people. Our patient was no exception. She had struggled with fear since childhood—fear of lightning, fear of her siblings, fear that she would lose her parents' affection, her husband's affection and her children's affection, and, finally, fear of death. Her prayers for death were interpreted as a need to deny her overwhelming fear of death. She was encouraged in her early marriage by her mother when she was emotionally unprepared for any attempt at an independent life. Her subsequent life had been one long struggle with her fears and dependent needs. The presence of specific phobias is characteristic of these patients, as Ficara [30] has shown. In fact, Lewis [19] has described exophthalmic goiter as "structuralized fear." It is interesting that all of the patients with thyroid storm whom Lidz has observed have been bizarre personalities, and that most of them are either potentially or actively psychotic before the storm.[31] McArthur [1] has made similar observations. In her series of patients with hyperthyroidism, Conrad [23] found a predominating tendency toward paranoid reactions, particularly in postmenopausal women. Our patient showed many of these traits, and under the stress of an overwhelming life situation she developed thyrotoxicosis and subsequent thyroid storm with frank psychosis.

Summary

The case history is presented of a patient with medical thyroid storm who recovered following medical and psychiatric treatment. The patient was a rigid, compulsive personality with phobias and psychotic tendencies who developed thyroid storm when faced with the disruption of the central interpersonal relationship of her life through which she satisfied her dependent needs for affection.

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DEMONSTRATION OF PULMONARY MIGRATION OF THE CAUSATIVE ORGANISM OF CREEPING ERUPTION *

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CREEPING eruption may be defined as an accidentally acquired disease which involves principally the skin. It is characterized by a linear, serpiginous eruption produced by migration of animal parasites within the skin. The classic lesion is a narrow, raised, erythematous formation along the course traversed by this

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† With the technical assistance of MR. STANLEY ABADIE.

parasite. Once the parasite has penetrated the skin it advances in random fashion, producing a well defined track. Intense pruritus is associated with this lesion.

The term "creeping eruption" was proposed in 1874 by Lee, who thought that the lesions were due to an "active parasite or animalcule" migrating in the skin. Crocker in 1893 thought that insect larvae produced the lesions. He proposed the term "larva migrans."

From 1895 until 1926 reports from various parts of the world were published which indicated that the disease could be caused by many different animal parasites. Larvae of the horse bot fly (Gasterophilus), the cattle grub fly (Hypoderma), pig and cat nematodes (Gnathostoma) and *Strongyloides stercoralis* were isolated. Even an ant was found in one case.

In 1926 Kirby-Smith, Dove and White,[1] working in the southeastern United States, succeeded in demonstrating another larva from a case of creeping eruption which they initially gave the name *Agamonematodum migrans*. In 1928 White and Dove [2] showed that these larvae were the third stage filariform larvae of the common dog and cat hookworm, *Ancylostoma braziliense* (de Faria, 1910). In 1929 White and Dove [3] and Shelmire [4] reported that *Ancylostoma caninum*, another dog and cat hookworm, could also produce creeping eruption. *Ancylostoma braziliense* has since been considered to be responsible for the majority of the cases of creeping eruption noted in the southeastern and southern sections of this country.

Humans acquire the disease when exposed parts of their bodies come into contact with soil containing infective larvae. The lesions have been observed on every portion of the body. The hands, buttocks and feet are most often affected. Most of the cases are contracted around swimming resorts, beaches, children's playgrounds or sandboxes. Plumbers, electricians and gardeners are commonly infected by working on or with polluted soil.

Once the parasites invade the skin they migrate, producing sensitive, pruritic papules and serpiginous tracks. The larvae are found in these burrows lying within the stratum germinativum, having the corium as a floor and the stratum granulosum as a roof. The larvae do not multiply or reach maturity within the skin of man.

Human intestinal infection with *Ancylostoma braziliense* or *Ancylostoma caninum* has occasionally been reported. These infections have been extremely light. In this country only one such case has been reported.[5]

Recently a patient was admitted to the Veterans Administration Hospital in New Orleans with creeping eruption. His complaints on entry were somewhat unusual, and subsequent study disclosed an heretofore unreported observation.

Case Report

Onset: The patient, a 57 year old white male, was admitted to the V. A. Hospital on July 23, 1951, with the following history. Twelve days before admission he had spent several hours under his house repairing a leaking water pipe. Forty-five minutes after finishing this work he became aware of an intense pruritus over the right lateral thigh and buttock. Within two days a diffuse papular rash developed over this area. The pruritus was not controlled by local remedies.

One week after this incident he developed a wheezing respiration, dyspnea and a cough productive of green tenacious sputum. His private physician told him that the symptoms were due to "asthma." In spite of adrenalin injections the symptoms persisted and were of such severity that his doctor referred him to the hospital with a diagnosis of "status asthmaticus." Prior to this time the patient had been in excellent health and had never been treated for respiratory or allergic disease.

Upon interrogation, the patient stated that when he repaired the water pipe he was attired in a thin pair of work trousers. When the work was completed, he found that his trousers had become wet at the point of contact with the ground. The pruritus

FIG. 1. Appearance of the skin lesions.

began shortly afterwards. According to the patient, the ground on which he worked was frequently the site of contamination with dog feces.

Physical Examination: On admission the patient was apprehensive and in moderate respiratory distress. The breath sounds were distant, the expiratory phase of respiration was prolonged. Numerous musical râles and rhonchi were heard bilaterally. A persistent cough was present, which was productive of tenacious sputum. An intense papular rash was seen over the right buttock and thigh. Several of the lesions were excoriated because of scratching but no secondary infection was present.

The entire area was very painful and pruritic. Emanating from several of the papules were red, elevated, tortuous tracks (figure 1).

Course in Hospital: On the night of admission a 12 hour sputum specimen was collected. The next morning, samples of this material were smeared over 2″ ×3″ glass slides and examined under low power. After two hours of careful search a motile nematode larva was found. Later several other similar larvae were observed (figure 2). A study of the larvae under high-dry magnification indicated that these were filariform ancylostoma larvae. The morphology of the larvae was not com-

FIG. 2. Ancylostoma larva in the sputum.

patible with that of *Necator americanus* or of *Strongyloides stercoralis*. It was thought that they were larvae of *A. braziliense*, the causative agent of creeping eruption, although the possibility of their being *A. caninum* could not be excluded. This conclusion was supported by the nature of the skin lesions. Furthermore, the infection was acquired under a house elevated only one foot above the ground, a site unlikely to be contaminated by human excreta.

During the first five days the patient remained in moderate respiratory distress and expectorated an average of 200 c.c. of sputum daily. The cough and chest symptoms then slowly regressed.

X-rays of the chest were done on the first, sixth and nineteenth days. All were reported as showing no evidence of pulmonary infiltration. Although the first hemogram was normal, succeeding studies disclosed a leukocytosis of 14,350 on the seventh day, with an eosinophilia of 24 per cent. These findings persisted for an additional two weeks.

Because of the intensity of the pruritus and pain, the lesions were sprayed lightly once with ethyl chloride. Several of the isolated papules were watched closely. Occasionally extensions of the papules in the form of slightly raised red tracks were observed. These could be palpated. They pursued an irregular, tortuous course and crisscrossed several times in random fashion. They did not extend over 2.5 cm. The lesions healed slowly without further treatment.

Multiple stool specimens were examined during the period of hospitalization and following discharge. The stool examinations covered a period of time which exceeded the average prepatent period of intestinal hookworm infection. No hookworm ova were found.

Daily sputum studies were done in the manner explained above. The larvae were found daily for 24 days.

Soil samples were obtained from beneath the patient's home. Third stage filariform hookworm larvae were easily demonstrated in these samples.

The patient was discharged, completely asymptomatic, on September 5, 1951, 44 days after admission.

Discussion

It has frequently been stated that the larvae of *Ancylostoma braziliense* remain in the stratum germinativum in human cases of creeping eruption. The finding of larvae in the sputum is unusual. To the author's knowledge such a finding has not previously been reported in this country.

In 1945 Wright and Gold [6] reported a series of cases of creeping eruption. In nine of their cases they noted the development of a transitory pulmonary infiltration with associated eosinophilia. Because of the paucity of clinical signs or symptoms to suggest systemic disease, the cases were reported as those of creeping eruption with Loeffler's syndrome. The authors did not state whether sputum studies were done. Although the procedure is easily performed, it is time consuming. It may be necessary to examine several smears or a relatively large volume of sputum to detect the larvae. Attempts to use concentration technics were considered unfeasible because of the tenacious character of the sputum.

It was thought that the patient's attack of asthma (another finding which is uncommon) was caused by the pulmonary migration of the hookworm larvae. It was felt that the multiplicity of respiratory symptoms and the absence of pul-

monary infiltration served to differentiate this case from one of Loeffler's syndrome.

The finding of the larvae in the sputum for 24 days was striking. This was undoubtedly influenced by the fact that intensive treatment of the skin lesions was not prescribed. A biopsy of one of the papules was not done, since the larvae were demonstrated in the sputum on the second hospital day.

As a result of observations in this case, it is suggested that more sputum studies should be done in cases of creeping eruption, particularly in those having respiratory symptoms or associated Loeffler's syndrome. Asthma apparently is only rarely produced by this particular form of hookworm disease. The finding of larvae in the sputum of this patient raised the question whether the pulmonary findings in Loeffler's syndrome, when associated with creeping eruption, are allergic in origin from cutaneous infection or due to the presence of larvae which have reached the lungs.

Summary

A case of creeping eruption has been presented. The patient developed asthma one week after onset of the skin lesions. Examination of the sputum revealed the presence of filariform hookworm larvae, which were thought to be those of *Ancylostoma braziliense*, the common causative agent of creeping eruption. It has been held by many writers that the larvae do not migrate beyond the site of skin penetration. However, the finding of larvae in the sputum in this case for a period of 24 days indicates that they are not always confined to the skin. The patient did not develop intestinal hookworm infection. In order to follow the disease process, and with the patient's approval, no attempt was made to treat the lesions vigorously.

Acknowledgment

I wish to thank Dr. J. C. Swartzwelder, Consultant in Parasitology, Veterans Administration Hospital at New Orleans; Dr. R. Jung, Instructor in Tropical Medicine, Tulane University; and Mr. P. G. Contacos, Instructor in Parasitology, Tulane University, for their assistance in identification of the parasite and examination of the soil samples.

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ACQUIRED ARTERIOVENOUS FISTULA BETWEEN THE AORTA AND A PULMONARY ARTERY: REPORT OF A CASE IN WHICH RUPTURE OF A SYPHILITIC AORTIC ANEURYSM WAS RESPONSIBLE*

By DAVID W. LEVIN, M.D., *Norristown, Pennsylvania,* WILMER H. RANDEL, JR., M.D., *Astoria, N. Y.,* and FRANK RATNER, M.D., *Lewisburg, Pennsylvania*

THE syndrome of rupture of an aortic aneurysm into a pulmonary artery is extremely rare: only 90-odd cases have been reported to date. Antemortem diagnosis is even rarer, because clinicians have not had the entity sufficiently brought to mind. The following case is reported, primarily, to emphasize the existence of this pathologic condition, to point out that the diagnosis can be made prior to death, and to show how such a diagnosis can be made; and secondarily, to add one more case to the world literature which, as noted above, is minimal.

CASE REPORT

A 38 year old Negro male was admitted to the Medical Service of the Queens General Hospital for the first time on December 22, 1948, because of increasing exertional dyspnea, orthopnea and ankle edema of two months' duration. He presented a history of "inflammatory arthritis" of the knees and ankles at the age of 25, for which he spent two months in bed. For six months subsequently he had generalized malaise. At the age of 28 he received 27 arm injections for primary lues. He also had gonorrhea at that time.

On physical examination the heart revealed the point of maximal impulse to be in the sixth intercostal space, just within the anterior axillary line. A thrill was palpable in the fourth intercostal space at the midclavicular line. There was a regular sinus rhythm; P_2 was louder than A_2. There was a harsh systolic murmur at the aortic region. A_2 was markedly diminished. In addition, a blowing diastolic murmur was heard at Erb's point. A rumbling diastolic murmur with presystolic accentuation, at well as a systolic murmur, was heard at the apex. MI was loud. The liver was palpated one fingerbreadth below the right costal margin. Patient had slight pretibial edema and slight clubbing of the fingers. The blood Wassermann test was 4 plus. An electrocardiogram showed regular sinus rhythm and minor T-wave changes in the precordial leads, and was interpreted to be an electrocardiographic expression of left ventricular hypertrophy.

He was placed on a salt-free diet and digitalized, and was maintained on digitalis and intermittent mercurial diuretics. His response was prompt and he was discharged to the Cardiac Clinic with the diagnoses of rheumatic heart disease (inactive), with enlarged heart, mitral stenosis and insufficiency, aortic insufficiency and minimal congestive failure, and latent lues.

Several routine blood cultures were taken during this hospitalization. Subsequent to the patient's discharge to the Cardiac Clinic, one of these cultures was reported to have grown out *Streptococcus viridans.* For this reason he was recalled on January 4, 1949.

* Received for publication September 6, 1952.

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Physical examination on the second admission was essentially the same as on discharge. Blood cultures were repeated and all were reported as sterile. A roentgenogram of the chest (figure 1) showed moderate cardiac enlargement, but the contour did not suggest any type of carditis. There was no abnormal widening of the aortic arch.

The patient was therefore discharged on January 14 to return to the clinic. At this time his general condition was good and his heart was apparently well compensated.

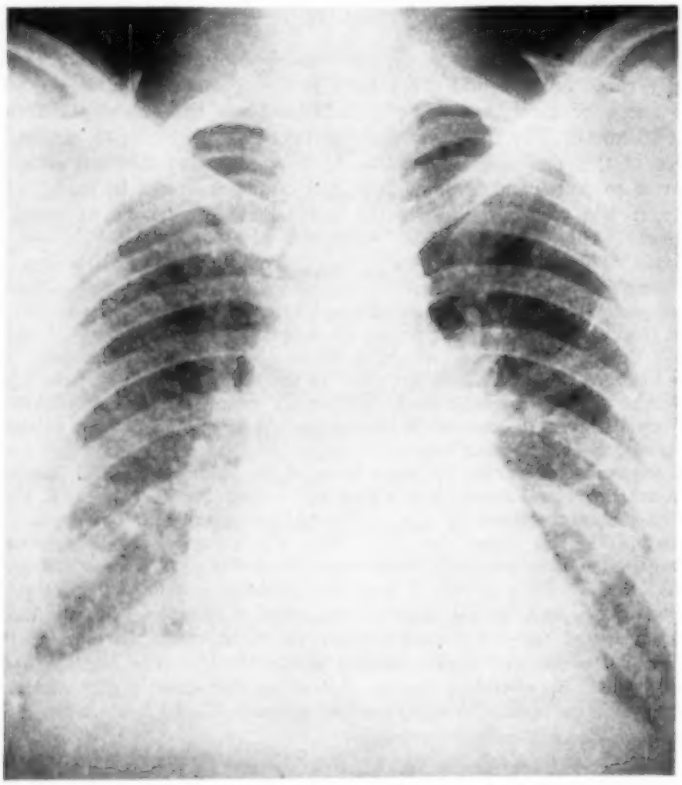

FIG. 1. Roentgenogram of chest (January 10, 1949). Note cardiac enlargement and prominence in region of pulmonary artery segment along left cardiac border.

He was admitted for the third time on February 20 because of an annoying, intractable dry cough, as well as dyspnea, orthopnea and ankle edema. In the interim he had apparently taken his therapy irregularly and had not adhered to a salt-free diet.

Physical examination on this admission revealed a well developed, well nourished Negro male, of approximately his stated age of 38 years, appearing acutely and chronically ill, with a severe dry hacking cough, and moderate dyspnea and orthopnea. The temperature was 97.2° F.; pulse, 112 per minute and regular. The respirations

were 24 per minute. The blood pressure was 152 mm. Hg systolic and 62 mm. diastolic. His face was puffy and the neck veins were markedly distended, filling rapidly from below. No abnormal pulsations were present. There was no prominence of the chest in the region of the precordium. The lung fields revealed an occasional râle at the right base.

Examination of the heart revealed the point of maximal impulse to be in the sixth intercostal space at the anterior axillary line. Regular sinus rhythm was present. There was a harsh grade 3 systolic murmur at the aortic region transmitted to the

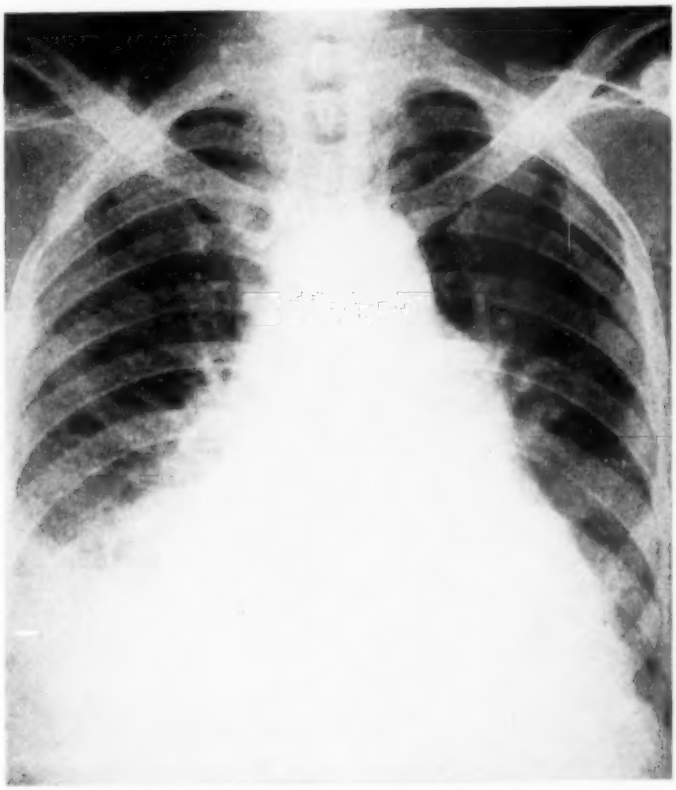

FIG. 2. Roentgenogram of chest (February 23, 1949). Note the increasing size of the pulmonary artery segment.

neck. No thrill was present. P_2 was loud and snapping, and greater than A_2. There was a to-and-fro murmur throughout systole and diastole, of greatest intensity at the second intercostal space, 2 cm. to the left of the sternum, transmitted toward the left shoulder and the back. In addition, there was a rough murmur beginning just after the second heart sound and continuing until the next second sound in the fourth intercostal space, 3 to 4 cm. to the left of the sternum. M1 could not be distinguished.

The remainder of the physical examination revealed the following: The abdominal

wall was slightly edematous and there was 3 plus presacral edema. The liver was palpable two fingerbreadths below the right costal margin but did not pulsate. No other organs or masses could be palpated. Four plus edema of the lower extremities extended up to the knees; 1 plus clubbing was apparent. No subungual splinter hemorrhages were noted. Rectal and neurologic examinations were not revealing.

Complete blood count and urinalysis were not remarkable. Blood Wassermann test was 4 plus. Innumerable blood cultures were sterile.

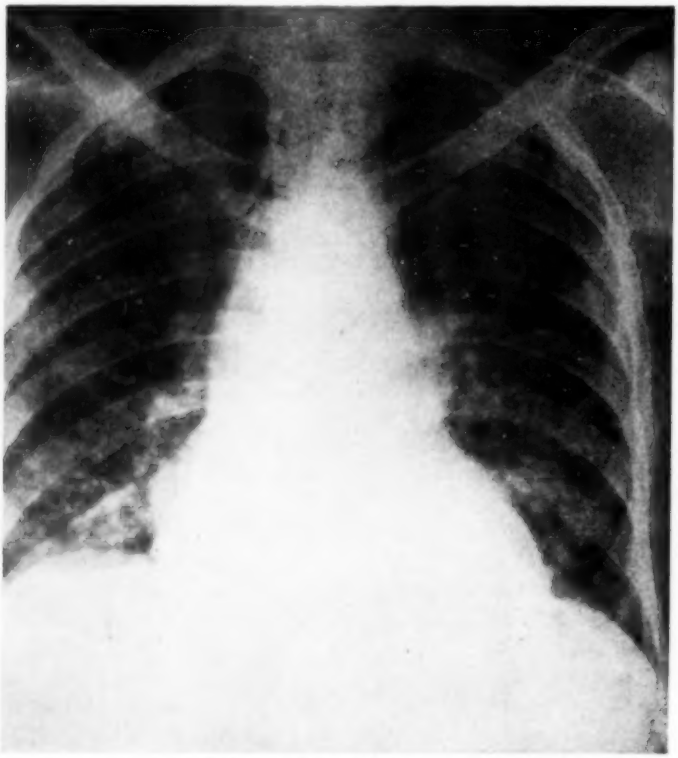

FIG. 3. Roentgenogram of chest (March 31, 1949). Note decrease in the size of the cardiac silhouette, with greater prominence of the pulmonary artery segment.

An electrocardiogram taken shortly after admission showed little change from previous tracings, revealing left axis deviation with a left heart strain pattern. A roentgenogram of the chest (figure 2) taken three days after admission revealed an increase in the size of the cardiac silhouette. The pulmonary artery segment was then prominent.

Saccharin circulation time, arm-to-tongue, was 23 seconds. Ether circulation time, arm-to-lung, 12 seconds. Immediately after the injection of ether the patient complained of numbness in the left hand and leg.

The impression now was (1) rheumatic heart disease (inactive), with enlarged heart, mitral insufficiency and stenosis, aortic insufficiency, and marked congestive failure; (2) lues, with possible luetic aortitis; (3) luetic aneurysm of the aorta, with rupture into the pulmonary artery.

The patient's cardiac status gradually improved and the cough decreased after intensive use of mercurial diuretics. Another roentgenogram of the chest (figure 3) revealed decrease in the size of the cardiac silhouette, with greater prominence of the pulmonary artery segment. Approximately three weeks after admission, while

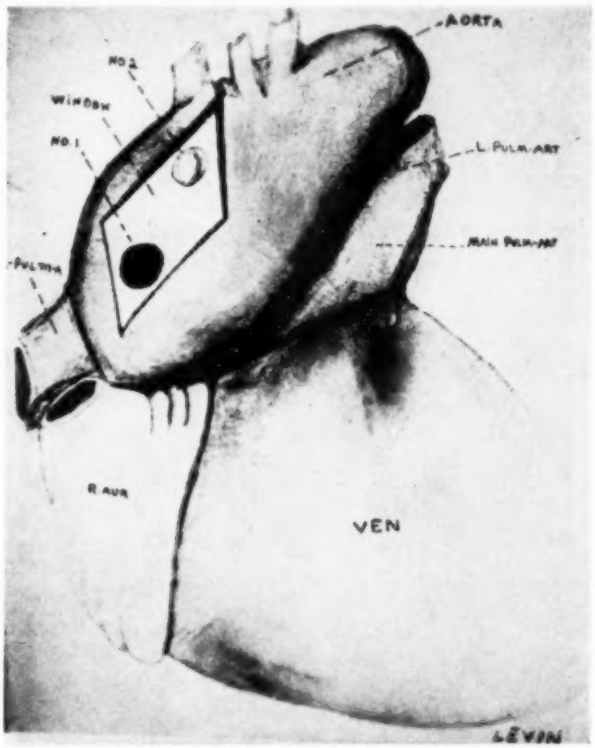

FIG. 4. Diagrammatic scheme of pathologic specimen. Note aneurysmal dilatation of ascending aorta, with cut-out revealing perforation into the pulmonary artery (No. 1) and beginning perforation (No. 2).

awaiting angiocardiography, the patient complained of abdominal pain associated with nausea and vomiting. Signs localized to the right lower quadrant. The white cell count was 8,000, with 80 per cent polymorphonuclear cells. Exploratory laparotomy was performed. An acute ruptured gangrenous appendix and a diffuse purulent peritonitis were found. The postoperative complication of a strangulated inguinal hernia developed, and the patient was operated upon under local anesthesia because of his poor condition. A large pelvic abscess was drained. His course was downward and he died on April 2, 1949.

Postmortem examination revealed the body to be that of a Negro male measuring five feet 10 inches in length and weighing approximately 160 pounds. There was no edema of any part of the body. The pleural and pericardial cavities contained no excessive fluid. The peritoneal cavity contained approximately 2 L. of fibrinopurulent fluid, with a fibrinopurulent exudate over the visceral organs. A large abscess cavity

FIG. 5. Pathologic specimen. Note arrows pointing to actual (I) and beginning (II) perforations, referable to No. 1 and No. 2 in schematic representation.

was found at the appendiceal site. There was enlargement of the liver, the organ weighing 2,000 gm. and extending 5 cm. below the right costal margin. The heart was markedly dilated, and right and left ventricular hypertrophy was present. The pulmonary artery and its branches were markedly dilated.

A large saccular aneurysm was found in the ascending portion of the aorta (figure 4). This sac was in communication with the right main branch of the pulmonary

artery through an orifice, 1 cm. in diameter, with smooth, well rounded edges (figure 5). The aperture was about 1 cm. beyond the bifurcation of the main pulmonary artery. The mitral leaflets were not unusual. There was fusion of the aortic cusps at the commissures. An anatomically patent foramen ovale was also present. The ligamentum arteriosum was isolated.

Microscopy revealed typical luetic aortitis. The juncture of the pulmonary artery and the aortic aneurysm showed a relatively smooth transition zone, with reactive changes along the edges (figure 6).

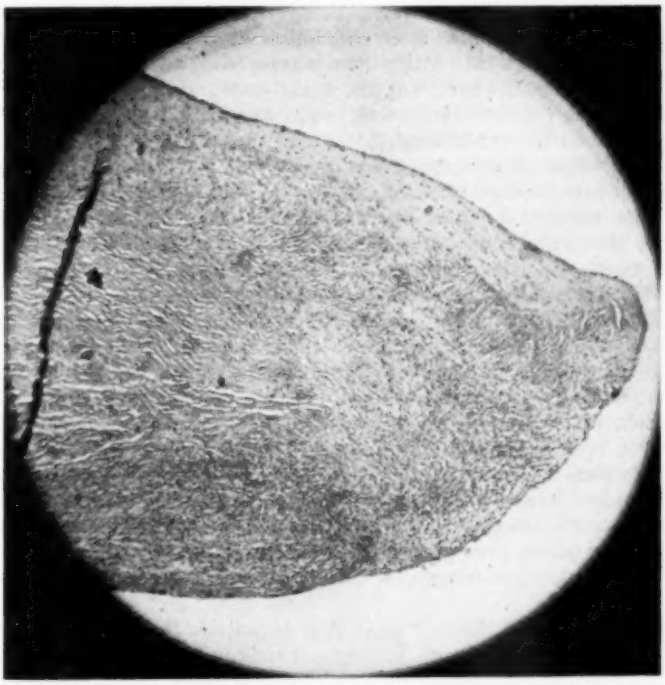

FIG. 6. Microscopic specimen (× 30). Juncture of pulmonary artery (below) and aorta (above), showing relatively smooth transition zone with reactive changes along edge.

DISCUSSION

Wells [1] reported the first case of rupture of an aortic aneurysm into a pulmonary artery in 1812. Until 1900 only 54 cases had been reported, and since then 36 cases have been added to the literature. Of these, only seven were correctly diagnosed ante mortem.[2, 3, 4, 5, 6] Considering the close anatomic relationship between the aorta and the pulmonary arteries, and the frequency of aneurysms of the ascending and transverse aorta, it is surprising that an arteriovenous fistula does not occur more often. This may be due to failure to recognize the condition clinically or to detect small perforations pathologically, or to the fact that aneurysms are more common in the anterior and right sides of the aorta than on the posterior or left sides.[7]

In 85 per cent of the cases reported the aneurysm was in the ascending aorta, and the aorta was usually bound down to the pulmonary artery by adhesions. There was usually marked dilatation of the pulmonary artery at the point of exit from the right ventricle, and the right ventricle was usually hypertrophied. When death had occurred suddenly, the walls of the vessels concerned showed a communication of variable size with ragged edges, but when rupture followed a slow erosive process the aperture presented smooth, rounded, epithelized edges.

Death may occur suddenly, or in several hours, or after many weeks or months. White et al.[4] reported a case in congestive failure for 21 months who lived for a period of eight months after the clinical diagnosis of rupture was made. Clerc et al.[8] reported a case with a four year survival after rupture. The average duration of life, however, was six weeks to four months. The duration of life after rupture depended upon the type of rupture, the size of the orifice, the amount of blood flowing through the orifice and the ability of the patient to compensate. For example, when rupture was sudden and the laceration great, there was a large amount of blood entering the pulmonary circuit and death resulted in a short time. Conversely, if the opening was small and occurred gradually the patient might live longer, although cardiac decompensation was usually present and rapidly progressive.

The clinical picture also would depend largely on whether rupture occurred suddenly or gradually. The classic picture is that of sudden onset of severe precordial pain at the time of rupture. This frequently follows some physical strain, such as lifting a heavy load, vomiting or coughing. Rapid and progressive dyspnea and orthopnea ensue. Edema, beginning in the lower or upper extremities, progresses to involve the entire body. Rasping cough with expectoration or hemoptysis follows. Cyanosis, with or without pallor of the face and extremities, frequently occurs. In addition, there are the physical findings of a continuous to-and-fro murmur in the pulmonic area, with or without the murmur of aortic insufficiency. If the erosion of the aneurysm into the pulmonary artery occurs more gradually the sudden pain at the onset may be absent, and the development of congestive failure and cough takes place over a period of months.

Thurman [9] in 1840, Hope [10] in 1839 in his classic *Disease of the Heart and Great Vessels (Munro's Case)*, Pepper and Griffith in 1890,[11] Clarke [12] in 1900, Hill and Rowlands [13] in 1912, Lewis and Drury [14] in 1923, and Porter [3] in 1942, after reviewing the various case reports, concluded that the salient features of this entity are as follows: There is continuous severe breathlessness, often with severe dry cough. Physical signs of pulmonary stasis are slight in proportion to the amount of dyspnea. Preponderance of right heart failure usually leads to marked and rapid anasarca. A systolic murmur and thrill, and a less intense and shorter diastolic murmur with or without a thrill, or occasionally a continuous murmur, are present over the second or third intercostal spaces to the left of the sternum. The latter murmur may resemble that heard in patent ductus arteriosus. The peripheral manifestations of aortic insufficiency are present. The history and laboratory findings of lues and/or x-ray evidence of aneurysm of the aorta are present. The clinical picture may occur suddenly with chest pain leading to collapse, dyspnea and edema. Sudden death or congestive failure is not uncommon. Klein and Porter [6] report that the pressures in the right

ventricle and right auricle as determined by intracardiac catheterization are markedly increased. For an excellent and complete discussion of the various physiologic mechanisms involved in the development of the syndrome, the reader is referred to the article by Nicholson.[2]

In retrospect, it is apparent that the case presented fits the clinical picture of a gradually developing erosion of a luetic aneurysm into a pulmonary artery. This conclusion is supported by the demonstration at necropsy of a smooth, round aperture.

Because of the patient's history of inflammatory arthritis at the age of 25 years and the physical findings and x-ray evidence suggesting mitral stenosis and insufficiency, the presence of a rheumatic cardiac lesion was suspected. However, it was difficult to correlate the presence of a regular sinus rhythm and congestive failure with long standing mitral stenosis on the basis of rheumatic heart disease. The presence of valvular heart disease with a regular sinus rhythm, rather than auricular fibrillation, suggested the presence of luetic heart disease. Although the clinical picture could have been consistent with the syndrome of compression of the pulmonary artery by an aortic syphilitic aneurysm,[15] the presence of a left axis shift by electrocardiogram tended to negate this diagnosis. The findings were interpreted by one examiner as due to an arteriovenous fistula between the aorta and a pulmonary artery. The development of numbness in the left hand and left leg following the intravenous injection of ether seemed to corroborate the presence of a shunt.[16, 17] Angiocardiography was proposed, but before this procedure could be carried out the patient developed an acute appendicitis and died. However, an acquired A-V fistula was suspected during life because of the absence of the to-and-fro murmur on the first admission. The history of lues, and the presence of a positive blood Wassermann and a regular sinus rhythm with failure in an individual with valvular heart disease, together with the evidence in support of a diagnosis of an acquired A-V fistula, convinced us that the patient was suffering from an aortic aneurysm which had ruptured into a pulmonary artery.

Summary

1. A case is reported of gradually developing erosion of a syphilitic aneurysm of the ascending aorta into the right pulmonary artery.
2. The diagnosis was suggested during the life of the patient.
3. The clinical features and pathologic findings of this syndrome are described.

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THE PROLONGED WATERHOUSE–FRIDERICHSEN SYNDROME WITH RENAL AND MYOCARDIAL INSUFFICIENCY *

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WITH the availability of potent adrenal cortical replacement therapy, cortisone, and highly effective chemotherapeutic agents against the meningococcus, sulfadiazine and the broad spectrum antibiotics, a marked reduction in the mortality of the Waterhouse-Friderichsen syndrome was to be expected. However,

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it appears from the experience reported herein and that of others [1] that we have but escaped the Scylla of fulminating peripheral vascular collapse to run upon the Charybdis of renal and myocardial insufficiency. Marangoni and D'Agati [1] have emphasized the constant presence of renal insufficiency in the Waterhouse-Friderichsen syndrome, and demonstrated its second stage, prolonged anuria and azotemia following the resolution of shock by heroic therapy. In the two cases reported by these authors death eventually occurred, in association with signs of myocardial insufficiency following desoxycorticosterone and massive fluid therapy. As the lives of more patients with this syndrome are sufficiently prolonged, it seems probable that these signs will become frequent manifestations of the associated renal and myocardial damage. It is the purpose of this paper to present a patient manifesting the entire gamut of this syndrome, from fulminating shock through anuria to death in myocardial failure, and to discuss the pathogenesis and particularly the prophylaxis of the latter developments.

Case Report

A 22 year old white male was first seen in the Receiving Office of William Beaumont Army Hospital on the night of February 3, 1952. It was learned that this patient had been withdrawn and combative for approximately two days. Two hours before admission he talked incoherently, would not answer questions, spat on the floor and attacked officers and corpsmen who attempted to restrain him. When first seen he was delirious, confused and lethargic, but responded to painful stimulation. While in the Receiving Office, confusion increased and a petechial and purpuric rash appeared on the trunk, spreading to the extremities in 20 to 30 minutes. The temperature was 103.9° F., the blood pressure was 118/66 mm. of Hg, and the heart rate was 116/minute. There was marked stiffness of the neck, with flexion limited to 40 degrees. A spinal tap was performed which revealed cloudy fluid containing 40 white blood cells per cubic millimeter, all neutrophils, and numerous gram-negative diplococci. Culture of blood and spinal fluid later revealed meningococcus type II A, sensitive in vitro to penicillin, terramycin, aureomycin and chloromycetin.

Therapy was begun immediately, consisting of sulfadiazine, 2.0 gm. initially and 1.0 gm. every four hours intravenously, and crystalline penicillin, 300,000 units every three hours intramuscularly. An intravenous infusion of 5 per cent dextrose in water was begun on admission. One hour after admission, a rapid fall in blood pressure from 116/76 to 100/62 mm. of Hg was noted, accompanied by the appearance of cold, clammy and cyanotic extremities, and enlargement as well as increased numbers of petechiae. Intravenous plasma under pressure was commenced, and 300 mg. of cortisone were administered intramuscularly. The blood pressure quickly dropped to imperceptible levels, but was restored to approximately 70/40 mm. of Hg following one half hour of rapid intravenous plasma administration. Four hours after admission there was a second episode of gradual fall in blood pressure, which was corrected by additional plasma and blood. Thereafter, and for the next eight hours, there was improvement in the patient's general condition, and the blood pressure remained stabilized at approximately 80/60 mm. of Hg. Eight hours after admission an absolute eosinophil count revealed no eosinophils.

Approximately 12 hours after admission it was evident that marked oliguria was present, the patient having voided only 50 c.c. of urine during this period. Sulfadiazine was stopped, terramycin, 0.750 gm. every four hours, was commenced, and crystalline penicillin was increased to 500,000 units every two hours intramuscularly. Fluids were limited to 1,000 c.c. per each 24 hour period. For the next 12 hours there was no noticeable change in the patient's condition. Confusion, with alternating

periods of restlessness and lethargy, persisted. There had been no further increase in the size or number of petechiae after the third hour of hospitalization. Eighteen hours after admission the patient became rapidly and markedly dyspneic. Slight facial edema was apparent. Examination of the lungs failed to reveal any râles, but 24 hours after admission the liver was found to be palpable and tender 5 cm. below the right costal margin. Peripheral arm veins remained distended when elevated considerably above heart level. Auscultation of the heart revealed no murmurs; the sounds were of fair quality, and there was a marked sinus tachycardia. Electrocardiogram showed a prolonged QT interval and elevated RST segments in Lead II and Lead aVL. No conduction defects or T-wave changes consistent with potassium effects were noted. Because of the hepatomegaly, tachycardia and dyspnea, it was felt that cardiac insufficiency was present. It was considered possible that the bacteremia, which had undoubtedly been present, had resulted in a toxic myocarditis, with congestive failure as the direct result of damage to the heart muscle. More probable was the possibility that the circulation had been overloaded, as a result of the combination of anuria and an excessive intravenous administration of fluid. Total fluid intake subsequent to hospitalization and prior to the appearance of cardiac failure was approximately 5,000 c.c., including 1,000 c.c. whole blood and 1,500 c.c. plasma which, minus an estimated insensible water loss of 1,500 c.c., and an original deficit of at least 1,500 c.c., would mean that the circulatory volume had been maximally increased by approximately 2,000 c.c. It was felt that although this amount would not ordinarily cause congestive failure, in the presence of anuria and possible myocardial damage due to shock and infection such a progression might occur. With these considerations in mind, digitalization was commenced intravenously, using lanatoside C, 0.4 mg. initially and 0.2 mg. every four hours for four additional doses. Continuous oxygen therapy was instituted by mask, and fluids were further limited to 750 c.c. daily.

During the 18 hours after initiation of digitalization, gradual improvement in the congestive failure occurred. Forty-eight hours after admission there had been definite recession of the hepatomegaly, but moderate dyspnea continued. Anuria, present since admission, persisted. Thirty hours after admission, blood chemistry studies revealed a blood CO_2 of 23 vol. per cent, a blood urea nitrogen of 52 mg./100 c.c., and a blood chloride of 475 mg./100 c.c. It was considered possible that the low CO_2 combining power contributed to the persistent dyspnea, and therefore, with some trepidation, the administration of one-half molar sodium lactate was commenced intravenously. However, after 150 c.c. of this solution (sufficient to elevate the CO_2 only approximately 3 vol. per cent) had been given, dyspnea was found to be increased and it was discontinued.

Commencing 42 hours after admission there was a gradual temperature rise and a progressive lethargy, associated with short periods of marked restlessness and incoherent talking. There were occasional small hemoptyses and several thin, tarry stools. Catheterization revealed an additional 50 c.c. of urine, making a total of 100 c.c. excreted during the hospital course. Analysis revealed microscopic hematuria and albuminuria with a specific gravity of 1.010. Approximately 54 hours after admission there was a sudden change in the patient's condition, as evidenced by markedly increased dyspnea, with râles in both lung bases, increased hepatomegaly, axillary temperature of 105° F., and increased stupor, although the blood pressure remained stable at 100/80 mm. of Hg. This was quickly followed by cessation of respiration and extreme tachycardia, possibly ventricular flutter. The latter was unaffected by intracardiac procaine, and death occurred quietly a few minutes later.

At *autopsy*, performed within three hours of death, passive congestion of the visceral and peripheral tissues was an outstanding observation. Changes directly ascribable to the meningococcus were few: cultures from the myocardium, from

petechial skin lesions on the thigh and ankle, and from spinal fluid did not yield meningococcus, and in the leptomeninges there were few inflammatory cells, those present being predominantly histiocytes, many undergoing degeneration.

The kidneys were enlarged and edematous, each weighing 270 gm. More than 100 c.c. of urine had accumulated in the bladder. Microscopically, the principal renal lesion was found to be dilatation of all the tubules and glomerular spaces. This apparently had resulted from obstruction of many of the collecting tubules by hyaline casts. Only rare sulfa crystals were present. No residual damage was found in the distal convoluted tubules.

The heart was dilated and flabby and weighed 350 gm. Epicardial and endocardial petechial hemorrhages were similar to those present on most of the serosal surface. No endocarditic changes were present. The interauricular foramen was patent, though guarded. On microscopic study the changes associated with toxic myocarditis were found: interstitial edema, slight parenchymatous degeneration of the fibers, and more or less isolated inflammatory cells. A petechial hemorrhage in the subepicardial fat near the base of the right atrium had attained a diameter of 4 mm. and had destroyed nearly the whole thickness of the atrial myocardium at this point. Neither bacteria nor abscesses were demonstrated in the heart.

Passive congestion in the lungs was associated with pulmonary edema and at least one microscopic infarct. In the liver, centrolobular congestion had progressed to the degree of necrosis involving one third to one half of the liver lobules. Fatty change had occurred in most of the remaining hepatocytes.

The changes in the adrenal glands were less striking at this stage of the illness than might have been expected had death occurred earlier. But slight loss of substance of the cortical cells was found. Capillaries in the cortex and especially at the corticomedullary junction were engorged. About a few of these were radially elongated hemorrhages; no inflammatory-cell or reparatory response had occurred. Periadrenal petechial hemorrhage was present bilaterally.

Discussion

Much evidence has been accumulated to substantiate the central position of the adrenal cortex in the pathogenesis of the Waterhouse-Friderichsen syndrome.[2] Acute experimental adrenal insufficiency has been demonstrated to produce a similar, though more slowly progressive, clinical state, and severe stress has been demonstrated to produce the characteristic pathologic alterations in the cortex.[3] Rich [4] has demonstrated that these changes occur in every case of the syndrome and consist of pyknotic degeneration and loss of substance of the cell cords, beginning in the fasciculus prior to or without any local hemorrhage. Such alterations may be the sole adrenal abnormalities in certain cases of this syndrome, particularly in adults, but usually the shrinkage of the degenerating cords away from the perivascular spaces and the concomitant dilatation and endothelial damage result in the characteristic hemorrhage and dissection of the cell cords, which convert them into tubular structures filled with blood and fibrin. The resultant clinical syndrome of fulminating peripheral vascular collapse is presumably the consequence of this invariable adrenal cortical destruction occurring in the presence of overwhelming infection (which latter still constitutes the major danger of the disease state [5]). The effectiveness of cortisone, when combined with chemotherapy, in saving lives in this condition corroborates the essential rôle of the adrenal in the progression of the infection to peripheral vascular collapse.[6]

Marked hypotension, with cold, damp, cyanotic extremities, tachypnea and tachycardia, develops within a few hours of onset in most instances of this syndrome, and peripheral vascular collapse, with barely discernible to absent diastolic pressure, exists for minutes to hours prior to death; if life is prolonged by therapeutic measures, as in the case herein presented, only a partial restoration of vascular tension may be achieved for hours to days thereafter. Thus the kidney, as well as the brain and myocardium, is exposed to prolonged vascular insufficiency. It has been common experience that prolonged hypotension, regardless of etiology, results in renal tubular injury, with the frequent production of the syndrome of lower nephron nephrosis. Indeed, Van Slyke,[7] from his own experiences and those of the military during World War II, feels that shock may be classified in three groups with regard to its renal effects: (a) fulminating, severe shock, resulting in early death without discernible renal pathology, i.e., the classic Waterhouse-Friderichsen syndrome; (b) prolonged but less severe shock, which is corrected but produces residual renal pathology, i.e., the prolonged Waterhouse-Friderichsen syndrome with anuria; and (c) transient shock, which is completely corrected prior to the production of residual renal pathology, i.e., the Waterhouse-Friderichsen syndrome with complete recovery.

Van Slyke [7] has demonstrated that the renal injury associated with peripheral vascular collapse and known as lower nephron nephrosis is chiefly due to compensatory renal ischemia during hypotension. The resultant anoxic damage to the distal tubular epithelium is directly proportional to the duration of the ischemia, which may persist for long periods even though partial restoration of general vascular tension has been achieved. In addition, a threshold of injury seems to exist beyond which any degree of damage yields the same clinical result, an approximate 10 day period of total renal failure with complete anuria and retention of fluids, electrolytes and metabolites. It seems possible that during this period the damaged distal tubule and loop of Henle are nonfunctioning, and merely passively reabsorb all of the glomerular filtrate, and the filtration itself may be restored once the state of shock is overcome. In any case, renal ischemia due to peripheral vascular collapse seems to explain adequately the renal pathology and resultant insufficiency of this and similar cases without the suspected toxemia which Marangoni and D'Agati [1] felt explained these findings in their cases. We do not fully understand the interrelationship of the stress of bacterial infection and adrenal insufficiency, as Nelson has indicated,[8] but we probably can safely presume that the hypotension resulting from these two factors accounts for the consequent renal and circulatory manifestations.

The possible rôle of sulfadiazine in the production of this renal failure is difficult to ascertain. Though this drug has produced tubular damage and persistent anuria in sensitive persons, rarely does urinary crystallization in the nonsensitive produce more than transient hematuria and oliguria. Thomas,[9] in a review of 1,518 cases of sulfadiazine-treated meningococcal infections, noted no persistent renal injury which could be attributed to sulfadiazine, but considered that overdosage was common and should be avoided, and that the use of a sodium lactate solution was desirable to prevent urinary crystallization. Whether a synergistic effect upon the production of damage to the renal tubules may occur when sulfadiazine is used in the presence of renal ischemia is un-

known.[10] This possibility, however, warrants further investigation, careful consideration in the individual case, and at least temperance in the dosages of sulfadiazine usually prescribed in fulminating meningococcemia. For the present, no complete choice exists, as sulfadiazine remains the drug of choice to combat the most important part of the Waterhouse-Friderichsen syndrome, infection. Penicillin is clearly inferior,[11] evidence is accumulating which indicates that aureomycin is less effective,[12] and chloromycetin seems to offer no advantages in the clinical control of the meningococcus.[13]

It thus seems logical to assume that, rather than being toxic or iatrogenic, the renal failure of the prolonged Waterhouse-Friderichsen syndrome is due to hypotension and will constitute a major problem of such patients. Contrary to common belief, however, there is good evidence that uncomplicated lower nephron nephrosis does not constitute a major threat to life, and that with good conservative care recovery should be expected in the vast majority of cases.[14] Indeed, in the cases of prolonged Waterhouse-Friderichsen syndrome thus far reported,[1] death was apparently due to cardiac failure rather than renal insufficiency. In our own case, death was preceded by 36 hours of elevated venous pressure, hepatomegaly, dyspnea and tachycardia. It is probable that even under these circumstances the dangers of renal insufficiency can be successfully controlled, and that the chief danger to life in those cases recovering from shock will be myocardial insufficiency.

Death in the course of lower nephron nephrosis is usually associated with signs of cardiac failure, dyspnea, basilar râles, hepatomegaly and edema.[15] In many cases, clear indication of excessive fluid therapy explains the marked expansion of the extracellular fluid compartment, particularly of the intravascular space, with resultant increase in cardiac work. Yeoman [16] has demonstrated the production of clinical cardiac failure in normal dogs by rapid intravenous infusions, and clinical experience has demonstrated similar occurrences in infants. However, it is probably the concomitant renal insufficiency in lower nephron nephrosis which, by preventing the usual distribution of excess fluid chiefly into the intracellular space, occasions a sufficient increase in cardiac work to produce clinical failure.[7] Any preëxisting myocardial disease or injury, such as the acute myocarditis which apparently existed in the reported case, will, of course, precipitate this reaction. In the Waterhouse-Friderichsen syndrome, cloudy swelling of the myocardium is almost always found at autopsy (even in the usual early cases), and is probably consequent to the myocardial ischemia associated with shock and possibly partly due to toxemia or actual myocardial infection. Certainly the myocardium is already weakened when exposed to the onslaught of a massive parenteral fluid intake without renal redistribution. If the fluid intake consists (as it must to correct the peripheral vascular collapse of this syndrome) of plasma and whole blood to expand the plasma volume, and of saline to expand the extracellular fluid compartment, the most damaging effects on the myocardium will result.[17] In retrospect, the administration of sodium lactate to correct an early metabolic acidosis in the presence of congestive heart failure in the case reported herein must be considered to have been inadvisable. The relatively large amounts of sodium necessary to correct this relatively innocuous acidosis, by adding even further to the overextended extracellular fluid structure, must be considered contraindicated. If metabolic ab-

normalities require correction exsanguination transfusion or the artificial kidney should be utilized to displace the retained anions; under no circumstances should further cation extension through the administration of sodium be permitted.[18] Friedberg [18] has recently analyzed this relationship and concludes that in the presence of renal insufficiency an even far less than normal sodium intake, with consequent expansion of the extracellular fluid compartment, may produce cardiac failure. In the case reported herein, massive blood, plasma and crystalloid solution administration preceded the clinical appearance of cardiac failure, but the maximal intravascular fluid expansion probably did not exceed 2,000 c.c., an amount probably tolerable under normal circumstances. With the renal safety valve lost and a possibly damaged myocardium, the administration of relatively small amounts of fluids to persons with lower nephron nephrosis carries a relatively great degree of risk.

The role of potassium in the production of this myocardial insufficiency is probably slight. The expected hyperpotassemia of renal insufficiency, with delayed myocardial conduction and eventual cessation of cardiac contractions, does not appear until many days after onset (if at all), and there was no evidence that such existed in the reported case. Subsequent to the great stimulus of administered cortisone, the normal level of extracellular potassium, which was demonstrated by the electrocardiogram, probably indicates the relative inability of the body to redistribute fluid and electrolytes between the intracellular and extracellular compartments in the presence of renal failure (as suggested above).

The possibility that cortisone administered in our case, or desoxycorticosterone in Marangoni and D'Agati's [1] cases, contributed to the cardiac failure must be considered. Expansion of the extracellular fluid compartment, associated with a slightly excessive intake of desoxycorticosterone and salt, has been demonstrated to produce clinical cardiac failure during the course of Addison's disease.[19] It is assumed that the myocardium, already weakened by the disease state, is unable to withstand the load of increased blood volume, and that a rise in venous pressure, hepatomegaly and pulmonary edema follow.[20] The fluid retaining properties of these drugs probably add little further risk in the presence of renal failure, but they certainly do nothing to assist the body in decreasing myocardial strain.

The production of myocardial injury by the meningococcus itself during the Waterhouse-Friderichsen syndrome is quite possible, but has not been definitely detected at autopsy in any of the cases reported. In a complete review of the cardiac complications of meningococcus infections, Weinstein [21] listed the occasional occurrence of myocarditis with or without myocardial abscesses, in addition to the more frequent pericarditis and endocarditis. There seemed to be no correlation between the severity of the systemic infection and the production of myocarditis, which in some cases appeared long after the initial infection had apparently subsided. Myocarditis of some degree was detected in 22 per cent of 156 cases of fatal meningococcemia by Daniels.[22] Electrocardiographic changes consistent with myocarditis in our case made us suspect this possibility before death, and microscopic examination suggested its presence at necropsy, but a full retrospective appreciation of the pathophysiology of this patient and the others reported leaves little doubt that the major cause for cardiac failure in this situation is the disordered state of the body fluids. However, a preëx-

isting or concomitant myocardial injury by the meningococcus cannot be ruled out clinically or pathologically and may indeed be a factor in predisposing to the yielding of the myocardium.

Thus it appears that it is precisely the therapy which we so heroically undertake to thwart the peripheral vascular collapse of the Waterhouse-Friderichsen syndrome, which finally causes the death of the partially restored victim in myocardial failure. It even appears probable that, were it not for this cardiac complication, almost all patients would recover in whom intravenous blood, plasma, electrolyte solutions and cortisone could restore vascular tension.[14, 18] And if we presume that the cardiac failure of this condition is due to the expanded extracellular fluid compartment, admittedly in the presence of myocardial injury and renal insufficiency, then the prevention of this fluid expansion seems the most essential part of the therapy of the patient whose hypotension was susceptible of correction but created a residual renal defect. Finally, we must admit that this expansion of the extracellular fluid compartment is of our own doing, and that its prevention therefore merely requires restraint from excessive fluid administration. The administration of those fluids most effective in restoring vascular tension by remaining intravascularly, i.e., blood and plasma, must be restricted to the minimum necessary, as they will be most potent later in maintaining increased cardiac work. This is only slightly less true of the administration of sodium. However, while it is true that no loss of intravascular fluid volume occurs in the Waterhouse-Friderichsen syndrome, the reëstablishment of normal proportions in the dilated vascular bed by the administration of fluid is an essential part of early therapy. It is singular that in this condition the administration of fluid to correct the initial intravascular disproportion is superimposed upon a normal intravascular fluid volume, which results, after the restoration of vessel tone, in an equal disproportion of intravascular volume but, in the opposite direction, an excess of intravascular fluid. We obviously cannot permit death from progressive shock, or the certain production of lower nephron nephrosis by only partial restoration of vascular tension in an attempt to prevent the possibility of later cardiac failure. Any fluid beyond the essential minimum is contraindicated, however. Whether restoration of vascular tension in the dilated system may be expected without overloading the restored system can be determined only by further experience with prolonged cases. It is to be hoped that the restorative effects of cortisone on the vascular bed may be able largely to replace massive fluid therapy, though the relatively delayed onset of action of this drug makes this unlikely. Cortisone without excessive fluid, even with renal insufficiency, should be of little danger to the myocardium, and should be used in maximally effective doses as soon as possible.

Many, if not most, cases of the Waterhouse-Friderichsen syndrome will continue to die in fulminating irreversible shock with massive adrenal destruction, others will recover completely, through the rapid restoration of vascular tension by chemotherapy, cortisone and cautious fluid administration, without residual renal insufficiency or consequent myocardial insufficiency. Whether, in the intermediate group with residual lower nephron nephrosis following exposure to prolonged hypotension, cardiac failure can be prevented by the limited use of parenteral fluids with cortisone remains to be seen.

SUMMARY

A patient with the Waterhouse-Friderichsen syndrome is presented who demonstrated lower nephron nephrosis and died in cardiac failure following restoration of vascular tension by cortisone and fluid administration. The pathogenesis of this progression is discussed, and it is considered probable that prolonged hypotension and renal ischemia produced the renal insufficiency, while excessive fluid administration during this phase produced the cardiac strain which, superimposed upon myocardial injury and failure of the renal control of body fluid balance, resulted in clinical cardiac failure.

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EDITORIAL

PRIMARY SYSTEMIC AMYLOIDOSIS

WHEN a clinical syndrome indicates involvement of several systems, the diagnostician thinks of disease processes with a widespread common denominator. The blood and blood vessels permeate every organ in the body; the lymphatic system is widespread; the endocrines, by virtue of their hormones, have far-reaching effects; metabolism is universal; connective tissue is common to all organs and systems; infectious agents can take root far and wide. The clinician therefore considers:

(1) *blood* diseases, such as leukemia, polycythemia, multiple myeloma, sickle cell anemia;
(2) *vascular* diseases, such as atherosclerosis, thromboangiitis obliterans, thrombophlebitis migrans;
(3) *lymphomatous* diseases, such as Hodgkin's disease, lymphosarcoma, sarcoidosis;
(4) *endocrine* and *metabolic* disorders, such as Addison's disease, hyperthyroidism, hemochromatosis, the lipidoses;
(5) *collagen* diseases, such as disseminated lupus, polyarteritis nodosa, generalized scleroderma, rheumatic fever;
(6) *infections*, such as tuberculosis, syphilis, brucellosis, subacute bacterial endocarditis.

In all polysystemic problems another entity, less susceptible to classification, should be considered—primary systemic amyloidosis. For the present, this disorder is probably best considered in a class by itself, though, with the predilection of amyloid for the media of arteries and for connective tissue, it might be grouped among either vascular or connective tissue diseases; or, in the absence of more precise knowledge, it might be loosely classified as a disturbance of metabolism.

Primary systemic amyloidosis has increased in importance in recent decades. It has been raised above the level of an academic exercise in postmortem diagnosis and is now often diagnosable during life thanks to chemical and biopsy procedures. That it is being recognized with increasing frequency is indicated by the following figures: though the disease was first described in 1886, yet in 1939 Koletsky and Stecher [1] were able to collect only 23 cases from the literature. By 1946, however, Eisen [2] was able to review 48 cases, and in 1950 the Higgins [3] summarized a total of 71.

With an increasing tempo of diagnosis during life, obviously more opportunities for investigating methods of treatment will arise, and we may

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perhaps be justified in hoping that the discovery of a successful form of therapy is not remote in this era of triumphant therapeutic progress. It therefore seems worth while to review some of the factors in the diagnosis of amyloidosis and to refer briefly to claims already made in its treatment.

The exact nature of amyloid is not established. Protein fractions and a sulfate-bearing polysaccharide have been identified, but the original belief that chondroitin sulfuric acid was a constituent has not been substantiated. Variability in the staining reactions of amyloid suggests that it is probably not a single chemical substance but a series of closely related protein compounds. Although amyloid "degeneration" is frequently spoken of, it is probably an inaccurate and even unfortunate term. It is more accurate and perhaps less discouraging to think of the abnormality as the infiltration of a foreign material rather than a degeneration; for an infiltration is presumably more reversible. The substance accumulates particularly between parenchymal cells and in connective tissues.

In contrast with the predilection of secondary amyloid to affect parenchymatous organs—spleen, kidneys, liver, adrenals—the primary form of the disease tends to involve organs of mesenchymal origin. Thus of such organs in order of frequency the heart, tongue, gastrointestinal tract and skeletal muscles are implicated. The "parenchymatous" organs are involved in only about a quarter of the cases.

The diagnosis of primary systemic amyloidosis may be missed because the clinician is unaware that certain symptoms are attributable to the widespread infiltration. First and foremost it should be remembered, as stated above, that the heart is the most frequently involved organ, and evidence of its failure is the most frequently encountered syndrome. In their analysis of 71 cases Higgins and Higgins [3] found congestive failure present in over half. Weiss [4] in 1939 considered primary amyloidosis, despite its rarity, important enough to be considered in the differential diagnosis of all cases of clinically obscure heart disease.

Apart from involvement of the myocardium, the coronary vessels may be implicated in the infiltrative process leading to coronary syndromes; or the valves may be affected simulating rheumatic or other valvulitis. Actual mitral and aortic stenosis have resulted from amyloid infiltration. The electrocardiogram usually shows non-specific changes interpretable as "diffuse myocardial damage" or "non-specific myocarditis"; there is a tendency to low voltage, axis shifts, flattening or inversion of T waves and prolongation of the P-R interval.

Among the cases reviewed by the Higgins [3] general muscular weakness was noted in half; weight loss and macroglossia were observed in two fifths of the cases; deposits in the skin and mucous membranes in a third; lymph node enlargement and pains in the limbs in about a quarter; hypertension in about a fifth. Purpura, abdominal pain, hematuria, pruritus, epistaxis, fever and hematemesis were noted in decreasing incidence.

[4] Weiss, S.: Diseases of heart and aorta which are not well recognized, M. Clin. N. Am. **23**: 1323, 1939.

Involvement of the intestinal tract may lead to constipation or, less often, to diarrhea. Anorexia, nausea and vomiting may result. Several instances of severe gastrointestinal hemorrhage have been recorded.

Dyspnea is a common symptom, as would be expected from the high incidence of congestive failure. But it may result from other lesions including tracheal or pulmonary infiltration, or from the secondary anemia which is sometimes present.

Other tissues which may be involved are the serous membranes—peritoneum, pericardium and pleurae. The autonomic nervous system may be implicated with resulting pupillary changes, difficulty in micturition and impotence. The peripheral nerves may be infiltrated with resulting signs of peripheral neuritis. The involvement of peripheral blood vessels may lead to ischemic syndromes such as intermittent claudication. The joints and bones may be extensively involved and pathological fracture may be the incident that brings the patient under observation.[1]

Of great importance, because they are so accessible for examination in a disease sometimes so difficult to diagnose, are lesions of the skin and mucous membranes. Goltz [8] has very recently compiled a comprehensive review of this subject, and much of the material in the next few paragraphs is derived from his excellent collation. Eisen [2] found that 19 of 48 cases of the primary disease had deposits in the skin.

The most common cutaneous manifestation of amyloidosis is hemorrhage. Such purpura may occur into what looks like normal skin or it may involve obviously infiltrated areas. Hemorrhages, as well as the other cutaneous manifestations of amyloidosis, appear to favor the upper half of the body. The immediate cause of hemorrhage is apparently vascular disruption by amyloid infiltration. In all reported cases where purpuric areas have been histologically examined amyloid has been demonstrated in the vessel walls.

More characteristic lesions are the translucent papules and plaques of varying size between 1 mm. and 2 cm. They are shiny and look almost vesicular, but palpation reveals them to be solid and waxy. Usually yellowish and lighter than the surrounding skin, when involved by hemorrhage they assume the varied colors of disintegrating blood. According to Goltz they occur most commonly on the eyelids, nasolabial commissures, clefts of the chin, at the sides of the base of the neck, in the axillae and in the anogenital region. Other less characteristic types of papules and subcutaneous nodules are also seen.

Diffuse infiltration of the skin may occur. Areas particularly affected by this type of involvement are the hands, feet, head and neck. Even larger areas may be diffusely infiltrated and these lesions have earned from various German authors such terms as "sclerodermic type," "pseudoscleroderma" and "scleroderma amyloidosum." Myxedema is sometimes simulated.

[8] Goltz, R. W.: Systematized amyloidosis: a review of the skin and mucous membrane lesions and a report of two cases, Medicine **31**: 381, 1952.

Lymph nodes may be involved in the infiltrative process and form large protruding tumors. Ulcerations in the skin, alopecia, changes in the nails and various other cutaneous lesions have also been reported.

All the mucous membranes contiguous to the skin have been reported as involved. Papules, similar to those seen on the skin, frequently occur in the buccal mucosa. Salivary and mucous glands may become infiltrated with resulting dryness of the mouth. The larynx may be affected diffusely or with nodular deposits leading to hoarseness. Infiltration of the tongue, with resulting macroglossia, is one of the most widely recognized features of primary amyloidosis. It is not by any means universal, however, and should not be over-emphasized. Eisen,[2] in his review, found it in only 20 of the 48 cases. When macroglossia occurs it may prove most distressing. It may produce dysphonia, dysphagia and sometimes interference with breathing. At times the tongue enlarges to such proportions that it fills the mouth and completely precludes eating.

The diagnosis of amyloidosis depends to a large extent on a knowledge of its varied symptomatology. When clinical suspicion has been roused, laboratory aids may be of immense value in establishing the diagnosis. The affinity of amyloid substance for congo red is well known. This fact has been widely utilized in the detection of amyloid in vivo since Bennhold introduced the congo red test for amyloidosis in Germany in 1923. It has come to be recognized that all brands of amyloid have not the same avidity for the dye and therefore some do not absorb as much of the injected substance as others. Hence, even in the presence of definite amyloidosis, the congo red test is sometimes falsely negative. The diagnostic demands of different workers have varied greatly between 40 and 100 per cent disappearance of the dye from the circulation in one hour.

The test as usually carried out involves the intravenous injection of 10 c.c. of a 1 per cent solution of congo red with blood samples collected four and 60 minutes later. The concentration of dye in these two specimens is compared and the percentage of dye which has disappeared from the circulation during the hour is thus calculated. While some dye may be lost in the urine in combination with protein, it has been shown that this amount is insignificant and cannot materially affect the interpretation.

Certain refinements, however, have been proposed. It has been shown that a considerable amount of congo red may be removed from the circulation by the avid amyloid in the four-minute interval following injection before the initial blood sample is taken. Thus the difference between the concentrations at four and 60 minutes may not give a complete measure of the amount of dye lost from the circulation and the result may be falsely "negative."

To obviate this it has been suggested that the initial specimen of blood be withdrawn after only two minutes.[6] A further, and more idealistic, re-

[6] Taran, A., and Eckstein, A.: The standardization of the congo red test for amyloidosis, Am. J. M. Sc. 203: 246, 1942.

finement is that proposed by Unger and his associates [7] in 1948. These workers suggest the calculation of the *theoretical initial concentration* rather than using a two- or four-minute specimen for comparison. Such a calculation, if reasonably accurate, renders of no consequence the early absorption of dye by amyloid during the initial mixing period. Another source of error is simultaneously removed: for it has been clearly shown that two to four minutes is not sufficient time for the even distribution of an injected dye. Indeed several groups of workers have demonstrated that such mixing requires 7.5 to 20 minutes, and sometimes even longer.

Unger and his colleagues [7] suggest a further modification. They found that the greatest difference in the curves of removal of congo red from the blood of amyloid and non-amyloid subjects was maximal at 30 rather than 60 minutes. They therefore suggest that a 30-minute specimen be used and that more than 35 per cent removal at this time (as compared with the *calculated* initial concentration) be the diagnostic criterion for amyloidosis.

Various biopsy procedures have been fruitfully used in diagnosis. For many years the liver has been a favorite site. Waldenström [8] first drew attention in 1928 to its value in following the progress of secondary amyloidosis. As the liver is apparently involved in a minority of the primary cases, and as it is a procedure not entirely without danger, liver biopsy is of limited value in primary amyloidosis. Fatal hemorrhage has followed needle biopsy of the liver in a case with marked amyloid infiltration.[9]

Selikoff and Robitzek [10] introduced gingival biopsy as an easy and safe procedure. They found amyloid deposits in the gingivae of 14 of 18 patients in whom the clinical diagnosis had been made with reasonable certainty. They believe this to be a valuable method and suggest that its greatest use may be in cases where other diagnostic measures fail.

In those cases of primary amyloidosis in which the kidneys are involved, estimation of the relative amounts of albumin and globulin in the spilled urinary protein may prove to be of some diagnostic value. The few available studies on this subject suggest that the proportion of globulin in the proteinuria of amyloidosis is increased in comparison with that of other proteinurias. Thus Geill [11] in Germany in 1929 found that in glomerulonephritis and lipoid nephrosis only about 10 per cent of the spilled protein was globulin, whereas in amyloid disease the globulin fraction was from 40 to 65 per cent of the total. In France, Lemierre [12] and his associates studied

[7] Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Study of the disappearance of congo red from the blood of non-amyloid subjects and patients with amyloidosis, J. Clin. Investigation **27**: 111, 1948.

[8] Waldenström, H.: On the formation and disappearance of amyloid in man, Acta chir. Scandinav. **63**: 479, 1928.

[9] Volwiler, W., and Jones, C. M.: The diagnostic and therapeutic value of liver biopsies; with particular reference to trocar biopsy, New England J. Med. **237**: 651, 1947.

[10] Selikoff, I. J., and Robitzek, E. H.: Gingival biopsy for the diagnosis of generalized amyloidosis, Am. J. Path. **23**: 1099, 1947.

[11] Geill, T.: Klinische Untersuchungen über Albumin und Globulin im Blut und im Harn bei Nierenkranken, Ztschr. f. klin. Med. **110**: 334, 1929.

[12] Lemierre, A., Leon-Kindberg, M., Cottet and Mahoudeau-Campoyer, D.: Sclérose amyloïde du rein a forme albuminurique simple. Azotémie aiguë terminale, Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 1769, 1931.

the urinary protein in a single case of amyloid disease with nitrogenous retention; three examinations of the urine showed the albumin to range between 62 and 83 per cent. In this country Hiller, McIntosh and Van Slyke [13] found the A/G ratio in the urine in a single case to be 1.5, whereas it was usually above 10 in nephrosis, between 5 and 10 in acute nephritis, and usually below 5 in chronic nephritis with urea retention.

There is some indication that the electrophoretic pattern of the serum proteins may prove to be of diagnostic value. Reiner [14] has recently published the electrophoretic curve from a patient with amyloidosis.

The potential reversibility of amyloid infiltration has been mentioned. Experimentally produced amyloid infiltration in animals can be made to regress. Patients with secondary amyloidosis have recovered. This is well recognized following elimination of an active suppurative process and, with the continued use of antibiotics, such recoveries should become more commonplace as time goes on.

Also well recognized are temporary remissions in the course of secondary amyloidosis in which the liver and spleen regress in size and edema and albuminuria disappear. The congo red test, however, remains positive and sooner or later the noted improvements retrogress.

More startling are claimed cures of secondary amyloidosis in the continued presence of the primary suppurative lesion. Grayzel and Jacobi [15] in 1938 reported 13 cases of amyloidosis in children secondary to chronic suppurative disease. These patients were treated with powdered whole liver extract by mouth. The authors claimed that eight of these children had been completely free of all clinical signs of amyloid for from 20 months to seven years. Clinical improvement occurred despite the continued activity of a suppurative lesion. They emphasized that the liver therapy must be persisted with, despite absence of clinical improvement, for at least three years in a dose of 4 to 8 grams three times daily, before failure is admitted. Albuminuria persisted in most cases long after the complete disappearance of the other signs and symptoms. The congo red test also remained positive at this stage. Seven years later Jacobi and Grayzel [16] were able to report that nine of their cases then showed no dye retention although albuminuria was still present in seven patients.

Whitbeck [17] gave powdered whole liver (12 grams daily) over a period of two years to seven children and noted that after 18 months the spleen and liver receded in five cases. Albuminuria and edema also disappeared, though the congo red test remained positive.

[13] Hiller, A., McIntosh, J. F., and Van Slyke, D. D.: Excretion of albumin and globulin in nephritis, J. Clin. Investigation **4**: 235, 1927.

[14] Reiner, M.: Application of electrophoresis to medical problems, M. Ann. Distr. Columbia **21**: 11, 1952.

[15] Grayzel, H. G., and Jacobi, M.: Secondary amyloidosis: results of therapy with desiccated whole liver powder, Ann. Int. Med. **12**: 39, 1938.

[16] Jacobi, M., and Grayzel, H. G.: Generalized secondary amyloidosis. A clinicopathological study of 84 cases, J. Mt. Sinai Hosp. **12**: 339, 1945.

[17] Whitbeck, B. H.: Liver meal in the treatment of amyloidosis, J. Bone and Joint Surg. **14**: 85, 1932.

Various authors have reported failures with liver therapy. Jacobi and Grayzel point out that an analysis of these failures reveals that a variety of liver extracts was used without animal experimentation to determine their potency for reversing amyloid infiltration, and that treatment was often persisted with for less than a year.

Harmon and Kernwein [18] contested the cures claimed by Grayzel and Jacobi [15] suggesting that only two of their originally claimed cures could be considered as such. This they based on the fact that considerable congo red retention and albuminuria persisted after clinically apparent cures had been obtained. Jacobi and Grayzel [16] reply, however, that they have never seen such marked regression of symptoms in untreated cases and that experimental work suggests that spontaneous disappearance of appreciable amounts of amyloid does not occur. In their treated cases 100 per cent congo red retention was a constant feature before treatment, and, as stated above, nine of these patients showed no retention of congo red at the time of submission of their last publication.

Cohen [19] in 1943 recorded his impression that liver therapy did not materially affect the outcome in his cases. Jacobi and Grayzel point out that his 23 patients who were treated with liver received a dose averaging the equivalent of 51 grams of powdered whole liver per week—in their opinion an inadequate amount. Their experience has led them to believe that the minimum effective dose is 84 grams per week and the optimum 150 grams per week. They describe their method of preparing a potent and palatable oral liver extract in two papers.[16, 20]

Apparently there have been no reports to date of recovery in primary systemic amyloidosis. There seems to be no real reason, however, to believe that this form of the disease is any less reversible than secondary amyloidosis. For the present, despite the probable differences in the composition of amyloid in the primary form of the disease, and in the absence of any more definitive form of treatment, insistent long term liver therapy on the lines laid down by Grayzel and his associates should presumably be persevered with. Meanwhile search for a more certain and more effective amyloidotropic agent should be pressed forward.

H. J. L. M.

[18] Harmon, P. H., and Kernwein, G.: Utility of the congo red test in diagnosis and in differential diagnosis, Arch. Int. Med. **70**: 421, 1942.

[19] Cohen, S.: Amyloidosis complicating tuberculosis—diagnosis, prognosis and treatment, Ann. Int. Med. **19**: 619, 1943.

[20] Loukides, J., Grayzel, H. G., and Jacobi, M.: A simple liver preparation orally effective in the treatment of human amyloid disease, J. Lab. and Clin. Med. **28**: 1321, 1943.

REVIEWS

Klinische Elektrokardiographie. 2nd Ed. By MAX HOLZMANN. 652 pages; 17.5 × 24.5 cm. Georg Thieme Verlag, Stuttgart. 1952. Price, Ganzleinen DM 69.60.

The second edition of Holzmann's book on clinical electrocardiography is probably one of the best and most comprehensive texts on the subject. This masterpiece by an astute clinician is the product of extensive experience, observation and critical analysis. The graphic interpretation is always discussed in relationship to the clinical picture.

Although the book is written for the practicing physician and cardiologist, the historical and technical aspects are very adequately covered. The electro-physiological basis of the book is presented most vividly. For the discussion of the normal electrocardiogram, extremity as well as chest leads, the author adheres to the conventional concept. However, there is, in addition, considerable presentation of the vector concept of electrocardiography with excellent diagrams. The reader is particularly impressed by the author's sound selection of important factual detail from the vast information available from the literature of several decades. Esophageal and intracardiac electrocardiography receive a brief but adequate description.

The clinical evaluation of electrocardiographic abnormalities reveals the author's mastery as clinician and electrocardiographer. The description and discussion are detailed but lucid throughout. Reading the 200 page section describing cardiac arrhythmias in their common and even most uncommon forms was a particularly delightful task. It is probably the best and most detailed discussion of the subject since Katz's text on electrocardiography and is the clinical counterpart to the classical monographs of Lewis, and Wenckebach and Winterberg.

The text is very clearly written. Illustrations and diagrams are excellent and well chosen. The bibliography is adequate although European references predominate. The book is a most valuable contribution and is highly recommended.

The English translation of this book has just been published.

A. G.

Some Common Psychosomatic Manifestations. 2nd Ed. By J. BARRIE MURRAY, M.A., M.D. (Cantab.), M.R.C.P., Diagnostic Physician, Tavistock Clinic. 285 pages; 13 × 19 cm. Oxford University Press, New York. 1952. Price, $3.75.

Dr. Murray describes some common psychosomatic conditions in diseases of the skin, eyes, alimentary tract and in rheumatic disorders, devoting his main interest to discussions of the effort syndrome and miner's nystagmus. The author's goal is to give the medical practitioner a realization of the existence and importance of the psychogenic origin of physical illness in some patients. Dr. Murray illustrates his discussions with his own experiences and supports them by reviewing the literature. He stresses the recognition of such states without going into the psychodynamics of the personality. Advice with respect to psychotherapy is given only to such an extent as can be carried out by the general practitioner. This book will be of value mainly to medical practitioners and to industrial physicians.

H. W. N.

Ophthalmic Pathology: An Atlas and Textbook. By JONAS S. FRIEDENWALD, HELENOR CAMPBELL WILDER, A. EDWARD MAUMENEE, T. E. SANDERS, JOHN E. L. KEYES, MICHAEL J. HOGAN and W. C. and ELLA U. OWENS; with the editorial assistance of HELEN KNIGHT STEWARD. 489 pages; 20 × 29.5 cm.

W. B. Saunders Co., Philadelphia; sponsored by the American Academy of Ophthalmology and Otolaryngology and the Armed Forces Institute of Pathology. 1952. Price, $18.00.

This work is a most valuable addition to ophthalmic literature, for it is the result of an unusual collaboration of world renowned authorities in the field of ophthalmology. These contributing authors have produced a volume which is both a pathologic atlas of ophthalmic disease with many excellent photomicrographs, and a well written text which gives a comprehensive coverage of the most modern and well accepted concepts of the pathology and pathologic physiology of the human eye.

We have available in this volume a most valuable teaching aid for hospital residents and a wealth of material which will be for many years the pathologic Bible for ophthalmologist and student alike.

F. E. K., Jr.

Carbohydrate Metabolism: Correlation of Physiological, Biochemical and Clinical Aspects. 2nd Ed. By Samuel Soskin, M.D., and Rachmiel Levine, M.D. 346 pages; 17.5 × 25 cm. University of Chicago Press, Chicago. 1952. Price, $8.50.

The second edition of "Carbohydrate Metabolism" is intended as a correlative text for the teaching of carbohydrate metabolism in courses of biochemistry, physiology, and medicine. The material, as in the first edition, is divided into five parts: I, The biochemistry and energetics of carbohydrate metabolism; II, Introductory physiological considerations; III, Critical survey of the classical criteria of diabetes; IV, The rôle of the endocrine glands in carbohydrate metabolism; and V, Integration of physiological and clinical aspects.

Although basic concepts have not changed radically in the past five years, research utilizing labeled atoms and research on tissue enzyme systems have increased the available information in various areas covered in the volume. This information has been incorporated into the text, charts and tables have been brought up to date, and new charts and tables have been added. The establishment of an active two carbon fragment in the central position in the intermediary metabolism of carbohydrate, fat, and protein has emphasized the desirability of integrating the discussion of the metabolism of all the foodstuffs. The evidence for gluconeogenesis from both fat and protein is discussed and the common pathway for the utilization of carbohydrate, fat, and protein is outlined.

This volume should be useful both as a text and as a reference volume for all those interested in metabolism.

M. A.

Congenital Anomalies of the Heart and Great Vessels. By Maurice A. Schnitker, M.D., F.A.C.P., Director of Medicine, St. Vincent's Hospital, Toledo, Ohio. 306 pages; 15.5 × 24.5 cm. Oxford University Press, New York. 1952. Price, $8.00.

This concise volume contains much useful information concerning congenital heart disease. The author first discusses the embryology, etiology and incidence of congenital cardiac disorders, and the pathogenesis of cyanosis and clubbing. The essential clinical and laboratory findings in a wide range of such disorders are then presented. The text is quite complete and well-organized, and the bibliography useful. It is therefore regrettable that this book contains no reproductions of electrocardiograms or roentgenograms, for this limits its usefulness, since such studies are very important in the diagnosis of congenital cardiac conditions.

S. S.

Renal Pelvis and Ureter. By PETER A. NARATH, M.D., F.I.C.S., Adjunct Professor of Urology, New York Polyclinic Medical School and Hospital. 429 pages; 17.5 × 26 cm. Grune and Stratton, New York. 1951. Price, $12.50.

This is a monograph on the embryology, detailed anatomy, physiology, and roentgenography of the renal pelvis and ureter. There are 27 pages of bibliography listed according to the year of publication beginning with the year 1677 and ending with papers of 1950. Fourteen pages are devoted to a review of the embryology which is illustrated by drawings of the human embryo at different stages. The next 133 pages are a discourse on the final form of the renal pelvis. There is a comparative description of the kidney structure in several different species of mammal. Pyelograms are shown to illustrate the several types of pelves and grouping of calyces in the human. Some of the pyelograms are shown in oblique view to point out the dorsal and ventral groups of calyces. The author classifies renal pelves by 7 "construction formulae" derived according to the distribution of dorsal and ventral calyces into the cranial, central, and caudal poles of the kidney. Other than that they are variations of normal, no apparent significance is attached to the differences in form. Forty six pages are devoted to the normal anatomy of the pelvis and ureter, and 18 pages are given to the histology of these structures.

A discussion of the dynamics of the upper urinary tract is presented along with a review of the literature on the subject. Pyelographic evidence is presented in support of the theory that there are a series of sphincters, the actions of which control the collecting and emptying phases of the upper urinary tract. The use of kymography, fractional ureterography, and fluoroscopy is emphasized. In a discussion of the "tonus of the urinary tract," the author presents his views on the response of the musculature of the tract to reflex stimuli, to drugs, to the autonomic system, and to the volume of urine excreted. Evidence from his own as well as other experiments is presented to show that certain compounds and elements are "absorbed and resorbed" through the "urothelium" of the upper urinary tract. Various forms of extravasation following filling of the tract are analyzed. Finally, there is a history and discussion of methods of roentgenographic study of the upper urinary tract.

There is doubt that all physiologists and urologists will agree with the author's conclusions on the structure and functions of the upper urinary tract. Nevertheless, the presentation is unique and thought-provoking. It is recommended for study to particularly the urologist and to anyone with an interest in the detailed anatomy and physiology of the renal pelvis and ureter.

J. D. Y., JR.

Gastrointestinal X-Ray Diagnosis. By MAX RITVO, M.D., Assistant Professor of Radiology, Harvard Medical School; Instructor in Radiology, Tufts Medical School; Director, Department of Radiology, Boston City Hospital; Associate in Radiology, Beth Israel Hospital, Boston, Mass.; and I. A. SHAUFFER, M.D., Instructor in Radiology, Harvard Medical School; Instructor in Radiology, Tufts Medical School; Visiting Radiologist, Boston City Hospital. 838 pages; 18.5 × 26.5 cm. Lea and Febiger, Philadelphia. 1952. Price, $20.00.

Gastrointestinal X-Ray Diagnosis is a new treatise dealing principally with the roentgen manifestations of lesions of the gastrointestinal tract and its related viscera. Principal emphasis is placed on the description, discussion and evaluation of these roentgen manifestations and the basis upon which a diagnosis can be established. Clinical and pathological findings are often discussed but only when needed for a more complete understanding of the subject. Brief considerations are often devoted to the differential diagnosis of various lesions but treatment is rarely mentioned. Methods and technical aspects of roentgen studies are discussed in detail.

This book is well organized and well written for easy reading. It is extremely well illustrated with multiple illustrations of the more common lesions. The bibliography is also very complete. From the roentgenological standpoint this book is more complete than the others previously available, though the authors do not propose to present any new entities. Although it is written primarily for the roentgenologist and gastroenterologist it will be quite useful to all physicians who are interested in the gastrointestinal tract.

J. M. D.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Basedow's Disease: The Manifestations, Timing, Duration and Outcome of Basedow's Disease; Symptoms, Severity and Age Incidence; The Disease in Children; and Its Occurrence Among Animals. By H. SATTLER, M.D., Professor of Ophthalmology, University of Leipsig, German; English translation by G. W. and J. F. MARCHAND. 605 pages; 23.5 × 15.5 cm. 1952. Grune & Stratton, New York. Price, $10.00.

Annotated Bibliography of Vitamin E, 1950 and 1951. Volume II. Compiled by PHILIP L. HARRIS and WILMA KUJAWSKI, of The Research Laboratories of Distillation Products Industries, Rochester, New York. 106 pages; 27.5 × 21 cm. (paper-bound). 1952. Distributed by The National Vitamin Foundation, Inc., New York. Price, $2.00.

Atlas of Medical Mycology. By EMMA SADLER MOSS, B.S., B.M., M.D., Director, Department of Pathology, Charity Hospital of Louisiana at New Orleans, etc.; and ALBERT LOUIS MCQUOWN, B.S., B.M., M.D., Pathologist, Our Lady of the Lake Sanitarium, Baton Rouge, Louisiana, etc. 245 pages; 26 × 17.5 cm. 1953. The Williams & Wilkins Company, Baltimore. Price, $8.00.

Beiträge zur Zellulartherapie. Festschrift zum 70. Geburtstag von Dr. Med. Paul Niehans, La Tour-de-Peilz, Schweiz. 132 pages; 22.5 × 15.5 cm. (paper-bound). 1952. Urban & Schwarzenberg, München-Berlin. Price, Ganzleinen DM 15.

Clinical Electrocardiography in Children. By GERTRUDE H. B. NICOLSON, M.D., Associate in Cardiology, Chief of Children's Cardiac Clinic and Assistant Visiting Physician to the Children's Service at St. Luke's Hospital, etc. 118 pages; 21.5 × 14 cm. 1953. The Macmillan Company, New York. Price, $3.25.

Clinical Electrocardiography: A Textbook for Practitioners and Students. By DR. MAX HOLZMANN (Zurich); translated by DOUGLAS ROBERTSON, M.A., D.M. (Oxon), M.R.C.P. (Lond.). 647 pages; 25.5 × 16 cm. 1953. Staples Press, New York. Price, $21.00.

Headaches: Their Nature and Treatment. By STEWART WOLF, M.D., Professor and Head of the Department of Medicine, University of Oklahoma School of Medicine; and HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology), Cornell University Medical College. 177 pages; 19.5 × 13.5 cm. 1953. Little, Brown & Company, Boston. Price, $2.50.

Infectious Mononucleosis. Modern Medical Monographs 5. By SIDNEY LEIBOWITZ, M.D., Associate Physician, Beth Israel Hospital, New York, N. Y. 163 pages; 22.5 × 14 cm. 1953. Grune & Stratton, New York. Price, $4.75.

Office Management of Ocular Diseases. By WILLIAM F. HUGHES, JR., M.D., Professor and Head, Department of Ophthalmology, University of Illinois College of Medicine, etc. 452 pages; 23 × 15 cm. 1953. The Year Book Publishers, Inc., Chicago. Price, $9.00.

Physiologic Therapy for Obstructive Vascular Disease. Modern Medical Monographs 6. By ISAAC STARR, M.D., Hartzell Research Professor of Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, Pa. 38 pages; 22.5 × 14.5 cm. 1953. Grune & Stratton, Inc., New York. Price, $2.50.

Poliomyelitis: Papers and Discussions Presented at the Second International Poliomyelitis Conference, Compiled and Edited for the International Poliomyelitis Congress. 555 pages; 26 × 18 cm. 1952. J. B. Lippincott Company, Philadelphia. Price: Limited number distributed without cost to medical schools, libraries and public health departments in this country and abroad.

Unipolar Lead Electrocardiography and Vectorcardiography, Including the Standard Leads, the aV and V Leads, the Cardiac Arrhythmias and the Principles of Vectorcardiography. 3d Ed. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, New York, etc. 601 pages; 24 × 15.5 cm. 1953. Lea & Febiger, Philadelphia. Price, $10.00.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. Hauptthema: Elektrokardiogramm. Edited by PROF. DR. RUDOLF THAUER, Bad Nauheim und Giessen. 334 pages; 23 × 15.5 cm. (paper-bound). 1952. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Kart. DM 40.—

Your Health, Sir! By MIRIAM LINCOLN, M.D. 211 pages; 19.5 × 13.5 cm. 1953. Harper & Brothers, New York. Price, $2.75.

COLLEGE NEWS NOTES

New Life Members

The College is pleased to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last list in the February issue of this journal:

Dr. Milton E. Bobey, Cleveland, Ohio
Dr. Lucien Waterman Ide, St. Joseph, Mo.
Dr. R. Emmet Kelly, St. Louis, Mo.
Dr. Gerardo M. Balboni, Boston, Mass.
Dr. Alexander George Davidson, Brooklyn, N. Y.
Dr. Charles H. Hiles, Wheeling, W. Va.
Dr. Julien E. Benjamin, Cincinnati, Ohio
Dr. Francis R. Dieuaide, New York, N. Y.
Dr. Grover C. Dale, Goldsboro, N. C.
Dr. Karl H. Doege, Marshfield, Wis.
Major General Arthur R. Gaines, (MC), USA, Ret'd, Philadelphia, Pa.
Dr. Edward Budnitz, Worcester, Mass.
Dr. Howard B. Carroll, Chicago, Ill.
Dr. Aime N. Fregeau, San Francisco, Calif.
Dr. William R. Gibson, Los Angeles, Calif.
Dr. John Richard Hamilton, Nassawadox, Va.
Dr. Lyle Motley, Memphis, Tenn.
Dr. Raymond M. Galt, Chicago, Ill.
Dr. Henry B. Kirkland, New York, N. Y.
Dr. John Peters, Oak Park, Ill.
Dr. William D. Province, Franklin, Ind.
Dr. J. Donald Milligan, Elgin, Ill.
Dr. Herbert R. Cammerer, Dayton, Ohio
Dr. Louis H. Sigler, Brooklyn, N. Y.
Dr. Howard L. Correll, Milwaukee, Wis.
Dr. Merlyn Carl Fred Lindert, Milwaukee, Wis.
Dr. Bruno J. Peters, Milwaukee, Wis.
Dr. Maurice A. Selinger, Washington, D. C.
Dr. Henry K. Taylor, New York, N. Y.
Dr. John Louis Garvey, Milwaukee, Wis.

ACP Postgraduate Courses

The following courses on the Spring, 1953 schedule have been concluded:

1. PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: Frank E. Bunts Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director.

2. STUDIES IN THE CLINICAL ASPECTS AND DIAGNOSTIC PROCEDURES IN CARDIOVASCULAR DISEASE: University of Southern California School of Medicine, Los Angeles, Calif.; George C. Griffith, M.D., F.A.C.P., Director.

Remaining courses on the schedule are as follows:

	March			April				May			
	9–13	16–21	23–27	Mar. 30–Apr. 4	6–11	13–17	20–25	27–May 2	4–9	11–16	18–22
Course No. 3. INTERNAL MEDICINE: SELECTED SUBJECTS: Cornell University Medical College and The New York Hospital, New York, N. Y.; David P. Barr, M.D., F.A.C.P., Director.	X			Easter Week—Easter, April 5	American Heart Assn. Meeting—9, 10, 11, 12 Atlantic City	Annual Session: American College of Physicians, Atlantic City					
Course No. 4. INTERNAL MEDICINE: SELECTED SUBJECTS: Mayo Clinic and Foundation, Rochester, Minn.; Drs. Arlie R. Barnes, Hugh R. Butt, Edgar V. Allen and William H. Dearing (all F.A.C.P.), Co-Directors.			X								
Course No. 5. CARDIOVASCULAR DISEASE, 1953: Philadelphia Institutions, Philadelphia, Pa.; William G. Leaman, M.D., F.A.C.P., Director.								X			
Course No. 6. CONTROVERSIAL ISSUES IN INTERNAL MEDICINE: The Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director.										X 11–15	
Course No. 7. ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M.D. (Associate), Director.										X 11–16	
Course No. 8. INTERNAL MEDICINE: IMPORTANT REFINEMENTS OF DIAGNOSIS AND TREATMENT: University of Oregon School of Medicine, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director.											X

Tuition fee for all courses except No. 7 is $30.00 for members, $60.00 for nonmembers. Course No. 7 is registered to capacity. Detailed course outlines and registration forms may be obtained from The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Advance Registration for Members, Atlantic City Annual Session, American College of Physicians

A special plan for advance registration of members of the College has been devised with the intention of facilitating registration at the Atlantic City Session, April 13–17, 1953. Success of the plan depends upon the full coöperation of members who plan to attend. Directions and forms accompanied the program. If any member who is going to attend the Session has not yet returned the advance registration form to the Executive Offices of the College, he should do so immediately.

ACP Regional Meetings

Northern New England: Hanover, N. H., March 14, 1953; Harry T. French, M.D., F.A.C.P., Governor for New Hampshire and General Chairman.

Southern Illinois: Bloomington, Ill., March 21, 1953; Charles H. Drenckhahn, M.D., F.A.C.P., Governor for Southern Illinois.

North Dakota: Fargo, N. D., September 12, 1953; Robert B. Radl, M.D., F.A.C.P., Governor.

Southeastern (Ala., Fla., Ga., S. C., Cuba): Sea Island, Ga., October 16–17, 1953; Carter Smith, M.D., F.A.C.P., Governor for Georgia and General Chairman.

Midwest (Ill., Ind., Iowa, Mich., Minn., Wis.): Milwaukee, Wis., November 21, 1953; Karver L. Puestow, M.D., F.A.C.P., Governor for Wisconsin and General Chairman; Francis D. Murphy, M.D., F.A.C.P., Milwaukee, Local Chairman.

North Carolina: Chapel Hill, December 3, 1953; Elbert L. Persons, M.D., F.A.C.P., Governor.

Eastern Pennsylvania: Philadelphia, January 15, 1954; Thomas M. McMillan, M.D., F.A.C.P., Governor.

At the appropriate time programs will be mailed to all members in the respective territories. Members from other regions may obtain copies of the program on request to the Executive Secretary of the College.

The 1953 Southeastern Regional Meeting

The States of Alabama, Florida, Georgia, South Carolina, and Cuba will conduct the Southeastern Regional Meeting of the College for 1953 at St. Simons, Sea Island, Georgia, at the King and Price Hotel, October 16–17. The mornings will be devoted to the Scientific Sessions, and the afternoons to recreational and social activities. Among the recreational activities will be fishing, golfing and sightseeing in this interesting and romantic Georgia coastal area.

The King and Price Hotel can provide 160 rooms, but reservations can also be made through them for nearby Motels. Individual reservations may be made at the Cloister also, for though they do not care to take care of the convention as a whole, they will be glad to take individual reservations.

The Committee for the meeting will be under the direction of Carter Smith, M.D., Governor for Georgia, with the assistance of the Governors for each State and for Cuba.

Coming Examinations by Certifying Boards

The American Board of Preventive Medicine, Ernest L. Stebbins, M.D., Secretary-Treasurer, 615 North Wolf Street, Baltimore 5, Md.

Examinations will be held for Certification on April 23, 24, 25, 1953, at the following Schools of Public Health:

University of California, Berkeley
Harvard University, Boston
Johns Hopkins University, Baltimore
University of Minnesota, Minneapolis
Tulane University, New Orleans

Examinations will also be held at the time of the annual meeting of The American Public Health Association in New York, Nov. 7–9, 1953.

The American Psychosomatic Society under the Presidency and General Chairmanship of Dr. Sidney G. Margolin (Associate), New York City, will hold its annual meeting at Haddon Hall, Atlantic City, April 18–19, immediately following the Annual Session of the American College of Physicians. Programs may be obtained from the Society's headquarters, 551 Madison Avenue, New York 22, New York.

The following meetings are announced:

AMERICAN RHEUMATISM ASSOCIATION—Waldorf-Astoria, New York, N. Y., May 28–29, 1953. Dr. W. H. Kammerer, Secretary, 33 East 61st St., New York 21, N. Y.

INTERNATIONAL CONGRESS OF RHEUMATIC DISEASES—Geneva, Switzerland, August 24–28, 1953. Write for information to: Dr. W. H. Kammerer, 33 East 61st St., New York, N. Y.

The Cook County Graduate School of Medicine announces a two-week intensive course on "The Diagnosis and Treatment of Congenital and of Rheumatic Heart Disease in Infants and Children," presented by Benjamin M. Gasul, M.D., and Egbert

H. Fell, M.D., and associates, from May 18 to May 30, 1953. For full information, write to: Registrar, Cook County Graduate School of Medicine, 707 South Wood St., Chicago, Illinois.

The National Paraplegia Foundation wishes to announce the continuation of a limited number of fellowships for research in spinal cord disease and trauma and in the complications commonly associated with such disease or injury. These fellowships carry a minimum stipend of $3000 per year and may be awarded to any candidate who has demonstrated a capacity for medical research and has outlined a program of meritorious study. The fellowships will be awarded by the Medical Advisory Committee and are open for award for the academic year 1953–1954. Application forms may be obtained from Dr. L. W. Freeman, Chairman of the Medical Advisory Committee, The National Paraplegia Foundation, Broad-Grace Arcade, Richmond 19, Virginia, and applications should be submitted to him not later than May 1, 1953.

Dr. Crawford N. Baganz, F.A.C.P., Manager, Veterans Administration Hospital, Lyons, N. J., announced in January that the Third Annual Institute in Psychiatry and Neurology would be held April 22–23, 1953, at the Hospital. Sponsored jointly by the Hospital, The New Jersey Neuropsychiatric Association and the New Jersey District Branch of A.P.A., the program will include clinical demonstrations and medical exhibits. Members of the College participating in the program include: Dr. Morris B. Bender, F.A.C.P., New York, "Simultaneous Tactile Tests in Normal and Abnormal Subjects"; Dr. Francis J. Braceland, F.A.C.P., Hartford, Conn., "The Relation of Endocrine Glands to Mental Disturbances," and Dr. Kenneth E. Appel. F.A.C.P., Philadelphia, "Modern Methods of Treatment in Psychiatry." In addition, Dr. Harvey J. Tompkins, F.A.C.P., Washington, D. C., will be one of the moderators. Those desiring to attend may obtain additional information from Dr. Baganz.

Two members of the College, in addition to those reported in previous issues of this journal, were honored at the annual meeting of the Mississippi Valley Medical Society, held last October in St. Louis. Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., Editor of the *Mississippi Valley Medical Journal and Radiologic Review*, received the 1952 American Medical Writers' Association Distinguished Award "for unusual and distinguished service to the medical profession." Dr. Wallis L. Craddock (Associate), Salt Lake City, was the winner of the 1952 Essay Contest for his paper entitled "Pulmonary Traits of the Systemic Mycoses."

Dr. Julius H. Hess, F.A.C.P., Chicago, recently received one of the nine Borden Awards for 1952. Professor Emeritus in Pediatrics at the University of Illinois College of Medicine and Senior Attending Pediatrician at Michael Reese Hospital, Dr. Hess was cited for "his many productive contributions to the care and management of the prematurely born infant."

Dr. Howard A. Rusk, F.A.C.P., New York, has been designated the recipient of the Dr. C. C. Criss award of $10,000 and a gold medal in recognition of his work in the rehabilitating of the physically handicapped. The award will be presented to Dr. Rusk during the Annual Session of the American College of Physicians in Atlantic City next month. In the announcement of the award, which is given by the Mutual Benefit Health and Accident Association of Omaha, it was stated that "Probably more than any other American, he has demonstrated that the physically handicapped can be taught to become socially and economically self-sufficient. . . . The

worth of salvaging human lives through his endeavors cannot be measured." Dr. Rusk is Director of the Institute of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center.

Dr. W. Cabell Moore, F.A.C.P., Washington, D. C., was recently awarded a certificate for meritorious service "to the medical profession and the District of Columbia" by the Medical Society of the District of Columbia.

Phi Delta Epsilon medical fraternity presented its distinguished service award to Dr. J. Roscoe Miller, F.A.C.P., Evanston, Ill., President of Northwestern University. The presentation was made to Dr. Miller during the recent annual convention of the fraternity in Chicago.

"Educator, author, humanitarian and complete pediatrician" was the tribute paid to Dr. Wilburt C. Davison, F.A.C.P., Durham, N. C., when he was recently honored in Chicago at a testimonial dinner given by fifty former members of the Duke Hospital staff who are now practicing in other parts of the United States. Dr. Davison, who is Dean and Professor of Pediatrics at the Duke University School of Medicine, was also signalized for his "significant accomplishments and many services to pediatric education."

Dr. Harry R. Litchfield, F.A.C.P., Brooklyn, N. Y., was awarded a "Presentation for Meritorious Service" on Jan. 26 by the Pediatric Section of the Medical Society of the County of Kings and the Academy of Medicine of Brooklyn.

Dr. George W. Covey, F.A.C.P., Lincoln, was recently appointed editor of the *Nebraska State Medical Journal.*

Dr. Maurice J. Costello, F.A.C.P., New York, was elected Vice President of the American Academy of Dermatology and Syphilology at the recent annual meeting in Chicago. Dr. John E. Rauschkolb, F.A.C.P., Cleveland, was reëlected Secretary-Treasurer.

Dr. George H. Coleman, F.A.C.P., has been made Secretary of the Institute of Medicine of Chicago, and Dr. Henry T. Ricketts, F.A.C.P., was reëlected as Chairman of the Board of Governors, of which Dr. Edwin F. Hirsch, F.A.C.P., is a newly elected member.

Dr. Edgar A. Haunz (Associate), Grand Forks, was elected Executive Secretary-Treasurer of the North Dakota Diabetes Association, which met recently in Fargo.

Dr. Ward Darley, F.A.C.P., Denver, Dean of the University of Colorado School of Medicine, was recently awarded the 1952 General Rose Memorial Hospital Citation. Dr. Darley is also President of the Association of American Medical Colleges.

Tufts College Medical School, Boston, has recently announced the appointment of Dr. Joseph M. Hayman, Jr., F.A.C.P., as Dean. In addition to his administrative duties, Dr. Hayman will also be Professor of Medicine at the College and Senior Physician at the New England Center Hospital. Dr. Hayman, who is currently Professor of Medicine at Western Reserve University School of Medicine, Cleveland, will assume his new duties April 1.

Dr. Herbert S. Gaskill, F.A.C.P., Indianapolis, Professor of Psychiatry at Indiana University School of Medicine, has recently been named Director of Psychiatric Services and Professor of Psychiatry at the University of Colorado School of Medicine, Denver.

Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Assistant Director, Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, has recently been appointed Chairman of the U. S. P. Anti-Anemia Preparations Advisory Board.

Dr. Hans S. Reese, F.A.C.P., Madison, has recently been elected a Corresponding Member of the German Society of Neurology.

At the annual meeting of the Southwestern Medical Association, Dr. Harold W. Kohl, Sr., F.A.C.P., Tucson, Ariz., and Dr. Leslie B. Smith, F.A.C.P., Phoenix, Ariz., were elected Vice Presidents.

Dr. George E. Burch, Jr., F.A.C.P., New Orleans, has become President of the Central Society for Clinical Research. Other officers for 1953 include Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Vice President, and Dr. Kenneth G. Kohlstaedt, F.A.C.P., Indianapolis, Secretary-Treasurer.

Among the officers elected at the annual meeting of the New Jersey Diabetes Association, held Jan. 14, Dr. George Ginsberg, F.A.C.P., Hoboken, was elected President, and Dr. George M. Knowles, F.A.C.P., Hackensack, Vice President.

Dr. Harold W. Lovell, F.A.C.P., New York, has been appointed by Governor Dewey to an advisory committee that will assist the State Mental Health Commission in planning a program for community services and research on alcoholism.

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Secretary-General of the College, has recently been named Chairman of the panel on shipboard and submarine medicine of the Committee on Medical Sciences, Department of Defense Research and Development Board. He succeeds Dr. Eugene F. DuBois, F.A.C.P., New York, who will continue to serve as a consultant to the panel.

Dr. Walter C. Swann, F.A.C.P., Huntington, W. Va., was recently appointed to the Executive Committee of the Pan-American Medical Association as a Vice President of the Section on Cardiovascular Diseases. During the recent shipboard meeting of the Association, Dr. Swann participated in panel discussions. Dr. Norton S. Brown, F.A.C.P., and Dr. Louis F. Bishop, Jr., F.A.C.P., New York, were also panelists.

Dr. Irving B. Brick (Associate), Washington, D. C., Assistant Professor of Medicine at Georgetown University School of Medicine, recently addressed the members of the Association for the Study of Liver Diseases at Chicago. His subject was "Residuals of Yellow Fever Vaccine Hepatitis after Ten Years—Medical and Legal Problem."

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, presented a paper entitled "Psychosomatic Aspects of Dentistry" at the meeting of the Harris Dental Society of Lancaster (Pa.) City and County, January 20.

Dr. J. H. Comroe, Jr., F.A.C.P., Philadelphia, delivered a Harvey Lecture on "The Functions of the Lung" in New York City last month. On March 9 and 10 in Boston, Dr. Comroe gave a series of four lectures in the American Trudeau Society's Course on Pulmonary Function.

Dr. Henry J. Tumen, F.A.C.P., Associate Professor of Gastro-enterology at the University of Pennsylvania Graduate School of Medicine, Philadelphia, served Feb. 11–14 as Visiting Consultant in Gastro-enterology at the Brooke Army Hospital, Fort Sam Houston, Tex. Dr. Tumen has recently been elected to a five-year term on the Subspecialty Board in Gastro-enterology.

Dr. Hobart A. Reimann, F.A.C.P., Visiting Professor of Medicine at the American University of Beirut, Lebanon, addressed the Middle East Branch of the British Medical Association on the subject "Periodic Disease" on October 10, 1952, and the Arab Medical Association on "Viral Dysentery" on November 29 in Jerusalem.

The Hartford (Conn.) Medical Society is currently sponsoring a series of biweekly lectures that are held Monday evenings at 8:30 in the Hunt Memorial Building. Dr. Chester S. Keefer, F.A.C.P., Boston, College Governor for Massachusetts, delivered the first lecture on Jan. 19, his topic being "The Practical Use of Antibiotics." Among the other guest speakers are Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, scheduled to speak March 16 on "Practical Considerations of Fluid Therapy," and Dr. Harold J. Jeghers, F.A.C.P., Washington, whose subject on April 20 will be "Differential Diagnosis of Jaundice and Application of Liver Function Tests."

Guest speakers at the Sixteenth Annual Meeting of the New Orleans Graduate Medical Assembly, held March 2–5, included: Dr. J. Lamar Callaway, F.A.C.P., Durham, N. C.—Dermatology; Dr. A. H. Aaron, F.A.C.P., Buffalo, N. Y.—Gastroenterology; Dr. Carl V. Moore, F.A.C.P., St. Louis—Hematology; Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn., and Dr. Henry A. Schroeder, Sr., F.A.C.P., St. Louis—Internal Medicine.

The 49th Annual Congress on Medical Education and Licensure was held in the Palmer House, Chicago, Feb. 8–10. In the meeting of the Advisory Board for Medical Specialties, Dr. Robin C. Buerki, F.A.C.P., Detroit, took part in the discussion of "One- and Two-Year Residencies," and Dr. Walter L. Palmer, F.A.C.P., Chicago, a Regent of the College, spoke on "Preceptorship Training in Lieu of Residency Training." Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., presided over the meeting of the Federation of State Medical Boards of the United States, of which Dr. Walter L. Bierring, F.A.C.P., Des Moines, is Secretary-Editor and Treasurer.

Dr. S. Howard Armstrong, Jr., F.A.C.P., Chicago, discussed "Private Patients in Medical Education" at the meeting of the Council on Medical Education and Hospitals, American Medical Association. Also at this meeting Dr. Joseph T. Wearn, F.A.C.P., and Dr. Thomas H. Ham, F.A.C.P., Cleveland, participated in the panel discussion on "The Evolution of an Experimental Program of Medical Education at Western Reserve University." In the afternoon session of the Council, Dr. Louis

H. Bauer, F.A.C.P., Hemstead, N. Y., Secretary-General of the World Medical Association, delivered a report on the "First World Conference on Medical Education." This was followed by a panel discussion, "The Internship in Modern Medical Education, Report of the Advisory Committee on Internships." Dr. Victor Johnson, F.A.C.P., Rochester, Minn., was the moderator, and discussants included: Dr. Armstrong, Dr. John C. Leonard, F.A.C.P., Hartford, College Governor for Connecticut, and Dr. John B. Youmans, F.A.C.P., Nashville, Tenn. Major General Harry G. Armstrong, (MC), USAF, F.A.C.P., The Surgeon General, and Dr. Stockton Kimball, F.A.C.P., Buffalo, N. Y., also participated in a panel discussion on "The Continuing Impact of the National Defense Program on Medical Education."

Dr. Dwight L. Wilbur, F.A.C.P., Clinical Professor of Medicine at the Stanford University School of Medicine, San Francisco, will be guest-participant in panel discussions at the First Western Hemisphere Conference of the World Medical Association at Richmond, Va., on April 24, 1953.

The sessions will provide opportunity for a discussion of current medical problems between representatives of the national medical societies of Latin America and United States specialists and practitioners. Dr. Louis H. Bauer, F.A.C.P., President of the American Medical Association and Secretary-General of the World Medical Association, will be moderator at a general session at which panel reports will be made.

Dr. Wilbur will contribute a chapter on recent advances in internal medicine to a volume commemorating the conference. He was born at Harrow-on-the-Hill, England, and is a graduate of the University of Pennsylvania School of Medicine.

Dr. Paul Dudley White, F.A.C.P., Boston, recently delivered the First Annual A. Murat Willis Oration before the Richmond (Va.) Academy of Medicine. His subject was "Personal Experiences in Cardiology."

Dr. Jacob M. Ravid, F.A.C.P., New York, participated in a Symposium on Cirrhosis of the Liver and presented a paper entitled "Histopathologic Aspects of Cirrhosis of the Liver with and without Ascites" before the section on surgery at the New York Academy of Medicine, New York, December 5, 1952.

A Symposium on Cardiovascular Diseases was sponsored by the Richmond (Va.) Chapter of the American Heart Association on Feb. 6. Speakers and their topics included Dr. Gordon B. Myers, F.A.C.P., Detroit, "The Pitfalls in the Electrocardiographic Diagnosis of Myocardial Infarction," and Dr. Robert L. Levy, F.A.C.P., New York, "The Management of the Patient with Coronary Heart Disease." Dr. Howard B. Sprague, F.A.C.P., Boston, addressed the evening gathering on the general subject of heart disease.

Dr. Paul S. Rhoads, F.A.C.P., Chicago, addressed the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, which was held in Chicago, Jan. 19. He discussed the "Joint Rôle of the Otolaryngologist and Internist in the Removal of Focal Infection."

"Recent Advances in Gastro-enterology" was the topic used by Dr. Joseph B. Kirsner, F.A.C.P., Professor of Medicine at the University of Chicago School of Medicine, when he delivered the Tufts Medical Alumni Lecture at the Tufts College Medical School, Boston, on Feb. 3.

Dr. Herrman L. Blumgart, F.A.C.P., Boston, Professor of Medicine at Harvard Medical School, spoke on "The Pathogenesis of Angina Pectoris and Some Clinical Implications" at the Michael Reese Hospital, Chicago, Jan. 23. His lecture was the first of a series on advances in medicine, sponsored by the Transparent Package Foundation of Chicago.

Dr. Samuel J. Weinberg, F.A.C.P., Los Angeles, discussed "The Influence of the Hypothalamus on the Function of the Heart and Kidneys" before the staff of the National Institute of Cardiology, Mexico City, Mexico, Dec. 16, 1952. The following day he delivered a similar lecture to the Medical Faculty of the University of Guadalajara, Jalisco.

Dr. Russell L. Cecil, F.A.C.P., New York, and Dr. James H. Means, F.A.C.P., Boston, were two of the participants in the program of the Fourteenth Annual Clinic Day, sponsored by Mt. Carmel Mercy Hospital, Detroit, Jan. 28. Dr. Cecil presented a paper entitled "Present Day Treatment of Chronic Arthritis," and Dr. Means discussed "Iatrogenic Vs. Theogenic Disease."

The House Officers' Association of New England Center Hospital, Boston, recently heard Dr. Robert F. Pitts, F.A.C.P., New York, and Dr. Lester R. Dragstedt, F.A.C.P., Chicago, in a series of evening lectures. On Jan. 30 Dr. Pitts talked on "Some Aspects of Acid Base Regulation," and on Feb. 20 Dr. Dragstedt spoke on "Some Contributions to the Physiology of Gastric Secretions and the Peptic Ulcer Problem."

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., a Regent of the College, served as moderator for a panel discussion on Blood Dyscrasias, which was presented by the Baltimore City Medical Society on Jan. 16. Dr. Milton S. Sacks, F.A.C.P., Baltimore, was one of the panel members.

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, Dr. Arthur C. Christie, F.A.C.P., Washington, D. C., and Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, were among those who participated in the Twentieth Annual Conference of Teachers of Clinical Radiology in Chicago, Feb. 7. Dr. Chamberlain and Dr. Christie were members of the panel that discussed "Radiologist-Hospital Relations and Arrangements for the Practice of Radiology in Hospitals"; Dr. Pendergrass was one of the discussants in the panel "Should the One- and Two-Year Residency Programs Be Abolished?"

Dr. Frederick L. McDaniel, F.A.C.P., Richmond, Va., has recently resigned his position as Assistant to the Commissioner of the State Department of Mental Health and Hospitals in order to accept a position on the Central Inspection Board of the American Psychiatric Association.

Dr. Daniel J. Glomset, F.A.C.P., Des Moines, has recently retired after more than forty years devoted to the practice of medicine. Dr. Glomset, who has been Consultant and Acting Head of Medicine at the Veterans Administration Center, will make his home in Santa Barbara, Calif.

Dr. Monroe J. Romansky, F.A.C.P., Associate Professor of Medicine at the George Washington University School of Medicine, Washington, D. C., and Consultant in Internal Medicine to the Surgeon General of the U. S. Army, recently

returned to the U. S. after a six weeks' tour of Army hospitals and installations in Germany and Austria. While abroad, he spoke before the Royal Society of Medicine in London, the Geneva Medical Society in Switzerland, and the Pasteur Institute in Paris.

The Hôtel-Dieu Hospital of Montreal has recently announced the creation of a new Clinical Research Department which will be in charge of Dr. Jacques Genest, F.A.C.P., formerly of the Johns Hopkins Hospital and the Rockefeller Institute for Medical Research.

This Department includes a five-room laboratory, a 24-bed unit, an outpatient department, and an animal room.

The main work will be devoted to the problems related to the mechanism of edema and of hypertensive disease as well as their relation to the sodium-retaining factor of the adrenals.

Dr. Louis Ochs, Jr., F.A.C.P., Clinical Assistant Professor of Medicine at Louisiana State University School of Medicine, has recently been named Chief of Gastro-enterology at Touro Infirmary, New Orleans.

Dr. George B. Eusterman, F.A.C.P., formerly Professor of Internal Medicine at the Mayo Foundation, Rochester, Minn., has recently been appointed Chief of Medicine and Director of Medical Education at the Sinai Hospital, Detroit.

St. Alexis Hospital, Cleveland, has recently announced the following appointments to its staff: Dr. Robert R. Bartunek, Sr. (Associate), Chief of Medicine; Dr. James F. Slowey, F.A.C.P., Vice Chief of Staff; Dr. Harry V. Paryzek, F.A.C.P., Honorary Staff.

Dr. Ralph M. Myerson (Associate) has recently been named Assistant Chief of Medicine at the Veterans Administration Hospital, Philadelphia.

Dr. Thomas Findley, F.A.C.P., College Governor for Louisiana, left on February 18, 1953, for a tour of medical facilities in Japan and Korea, on behalf of the Surgeon General's Office of the Army.

In the November, 1952, issue of the ANNALS OF INTERNAL MEDICINE there was given a list of members of the American College of Physicians who are presently in the Far East. Inadvertently omitted was the name of Col. A. E. White, (MC), USA, F.A.C.P., Commanding, 279th General Hospital.

Dr. Roscoe L. Pullen, F.A.C.P., Houston, has resigned as Dean and Professor of Medicine of the University of Texas Postgraduate School of Medicine to become Dean and Professor of Medicine of the University of Missouri School of Medicine, Columbia. Dr. Pullen's appointment becomes effective June 1, 1953. The University of Missouri is currently engaged in developing a new four-year medical school and university hospital.

Dr. Howard J. Hutter, F.A.C.P., has been elected President of the Society of Medical Jurisprudence of New York.

OBITUARIES

DR. ANGEL ARTURO ABALLI y ARELLANO

Dr. Angel Arturo Aballi y Arellano, F.A.C.P., died in Havana, July 22, 1952. Dr. Aballi was born in Matanzas, Cuba, on September 30, 1880. He graduated from the Institute of Matanzas in 1894 with A.B. and B.S. degrees and received his M.D. from the University of Havana Faculty of Medicine in 1901. Upon his graduation from Havana, Dr. Aballi undertook postgraduate work at the Carnegie Laboratories in New York City for a year, and the following year studied pediatrics in Berlin at the Kaiser und Kaiserin Friedrich Kinder Krankenhaus.

Dr. Aballi had been associated with the University of Havana Faculty of Medicine since 1895 when he became Nongraduate Instructor of Anatomy. He later became Assistant Professor of Medicine, Head of the Pediatrics Division, Professor of Pediatrics, and Emeritus Professor. He was appointed Dean of the University of Havana Faculty of Medicine in 1936.

At the Hospital Numero Uno and Hospital Mercedes, Dr. Aballi was Head of Pediatrics, and he was Technical Director of the Havana Children's Hospital.

He was a past President of the Society of Clinical Studies of Havana, the Medical Federation of Cuba, and the Cuban Society of Pediatrics; an honorary member of the Buenos Aires and New York Academies of Medicine, and a corresponding member of the Société Médical des Hôpitaux de Paris and of the American Pediatric Society. He had been a Fellow of the American College of Physicians since 1941.

A brilliant professor, Dr. Aballi influenced many generations, for his excellent teaching and administration gave rise to a very strong school of pediatrics. In addition, Dr. Aballi was one of the founders of the Medical Federation of Cuba, which has become the National College of Physicians, and was instrumental in founding the Havana Children's Hospital.

His loss is deeply felt not only by his colleagues but by his community.

DR. JOHN DE PAUL CURRENCE

Dr. John De Paul Currence, F.A.C.P., a Fellow of the American College of Physicians since 1942, died on October 20, 1952, of a dissecting aneurysm of the aorta.

He was born in Bullion, Mo., on July 9, 1899. He received the degree of B.S. from St. Louis University in 1925 and his M.D. from St. Louis University School of Medicine in 1926. Following this he interned at St. Mary's Hospital in East St. Louis (1925–26), was Resident in Medicine at Jackson Memorial Hospital (1926–27) and at Allison Hospital, Miami Beach (1927–28). He joined the staff of the New York Post-Graduate Medical School and Hospital in 1931 as Assistant Physician and Director of Physical Therapy. Later he became Assistant Clinical Professor of Medicine and Chairman of the Department of Physical Medicine. He was also Assistant Attending Physician in Physical Therapy at the Reconstruction Hospital and Associate Visiting Physician at the Welfare Hospital from 1939 until 1941. At the time of his death, Dr. Currence was Associate Clinical Professor of Rehabilitation and Physical Medicine at New York University College of Medicine.

Dr. Currence was a member of the New York County and State Medical Societies, the American Medical Association, the New York Academy of Medicine, the American Congress of Physical Medicine, the Association for the Advancement of Industrial Medicine and Surgery, the American Rheumatism Association, the American Therapeutic Society, the International Medical Society, the Pan-American Medical Society, and the New York County Physical Therapy Society.

Dr. Currence showed a continued interest in the development of the science of physical therapy and rehabilitation, and in this field he made his major contributions.

It was with sincere regret that the many friends of Dr. Currence learned of his passing at this time.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. J. DWIGHT DAVIS

Dr. John Dwight Davis, F.A.C.P., died December 15, 1952, in the Veterans Administration Hospital, Long Beach, Calif., where he had been Chief of the Pulmonary Disease Service for four years. He was born in Marion, S. D. on December 13, 1896, and was graduated from the University of Nebraska in 1919. He received his M.D. degree from the University of Illinois College of Medicine in 1922, and in 1929 was granted the M.S. degree from the Mayo Foundation.

After an internship at the Seattle City Hospital, Dr. Davis served as Senior Physician at the Muirdale Sanatorium, Wauwatosa, Wis., and as Medical Director of the Michigan State Sanatorium at Howell. He then studied at the Mayo Clinic from 1926 until 1929, when he moved to Los Angeles to become Senior Attending Physician, Tuberculosis Department, Los Angeles General Hospital. He also was Chief Visiting Physician at the Olive View Sanatorium, and was a member of the staffs of the Barlow Sanatorium, St. Vincent's Hospital and the Hollywood Hospital.

During World War II, Dr. Davis was on active duty with the Medical Reserve Corps of the United States Army; he served a four-year tour of duty and was discharged with the rank of Colonel. In May, 1946, he was appointed in the Department of Medicine and Surgery, Senior Grade, at the Veterans Administration Hospital, Van Nuys, Calif., and two years later was promoted to Chief Grade and became Chief of the Pulmonary Disease Service at the Van Nuys and Long Beach Veterans Administration Hospitals. In addition, Dr. Davis was Senior Consultant in Medicine at the Harbor General Hospital, Torrance, and had also been an Assistant Professor at the College of Medical Evangelists, and an Associate Clinical Professor of Medicine at the University of California School of Medicine in Los Angeles.

Dr. Davis was a member of the American Medical Association, National Tuberculosis Association and Phi Kappa Phi, Nu Sigma Nu and Sigma Xi fraternities. A Diplomate of the American Board of Internal Medicine, he had been a Fellow of the American College of Physicians since 1929.

Concerning him, Vice Admiral Joel T. Boone (MC), USN, Retired, Chief Medical Director of the Veterans Administration, has said:

"His professional achievements in the field of Pulmonary Diseases were well known nationally. His contributions throughout his medical career to Internal Medicine have been significant. This is evidenced by his great devotion to teaching, his contributions to literature and his personal service in the institutions of treatment and learning, from his residency in Chest Diseases in Washington, Wisconsin and Michigan, his Fellowship at the Mayo Foundation and later his term as Medical Director of the Olive View Sanatorium. His military service from June 8, 1942, to February 1, 1946, as an Internist and Administrative Officer also attests to his feeling of fellowship toward his fellow men and his country. The world and specifically the Veterans Administration can ill afford to lose men of his ability and culture."

DR. WILLIAM WHITE FALKENER

Dr. William White Falkener, F.A.C.P., was born February 20, 1892, in Warrenton, N. C. He received his A.B. degree from the University of North Carolina in 1912 and graduated from the University of Pennsylvania School of Medicine in 1915.

He had his internship at Children's Hospital in Philadelphia and was later Chief Resident at the Philadelphia Hospital for Contagious Diseases. He located in New-

port News, Va., beginning the practice of pediatrics there in 1921. He conducted an active and excellent pediatric practice in this city until his forced retirement on account of ill health in 1941. His death, which occurred September 8, 1952, was not, consequently, unexpected.

Dr. Falkener was an active participant in all of the medical affairs in his community and was on the staffs of the local hospitals. He had been Secretary and President of his county medical society, was a Diplomate of the American Board of Pediatrics and a Fellow of the American Academy of Pediatrics as well as a member of the state medical society and the Virginia Pediatrics Society. He became a Fellow of the American College of Physicians in 1937 and was proud of his membership in this organization.

Dr. Falkener was a respected and trusted consultant and enjoyed the friendship and admiration of all of his colleagues and patients.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

DR. HUGO A. FREUND

Dr. Hugo Abraham Freund, F.A.C.P., of Detroit, Mich., died on December 24, 1952, at Harper Hospital following a cerebral hemorrhage.

Dr. Freund was born in Detroit in 1881. Following graduation from the University of Michigan Medical School in 1905, he took postgraduate study at the University of Munich and, after a short period of serving as Assistant in Internal Medicine at the University of Michigan Medical School, he joined the staff of Internal Medicine at Harper Hospital. From that time on he had a long and distinguished career in this hospital, finally becoming Chief of the Department of Internal Medicine.

In addition to his work as a doctor, he was active in many civic affairs. He had served on the City of Detroit Health Commission and also the Public Welfare Commission. His leadership was important in the creation and the work of the Children's Fund of Michigan, which was started by the late Senator Couzens and of which Dr. Freund was a former President.

In addition to memberships in the county and state societies, Dr. Freund was a member of the American Medical Association and the American Association of Pathologists and Bacteriologists. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1926.

The profession of medicine and civic leaders in Detroit feel a great loss in Dr. Freund's death.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. OSWALD F. HEDLEY

Dr. Oswald Fenton Hedley, a Fellow of the American College of Physicians since 1940, died suddenly on November 18, 1952, in Washington, D. C. His death was caused by a coronary occlusion.

Dr. Hedley, who had been a member of the Commissioned Corps of the United States Public Health Service for 24 years, was Chief of the Public Health Office of the Mutual Security Agency at the time of his death. In 1947–48, he was Medical Director of the American Mission for Aid to Greece. Following that assignment, he served as Liaison Officer for the Economic Coöperation Administration until 1950, when he became chief medical officer of MSA.

Born in Danville, Va., May 18, 1903, Dr. Hedley received the degree of Bachelor of Science at the University of Richmond in 1925, and three years later took his medical degree at the Medical College of Virginia in Richmond. He served his internship in the Public Health Service Hospital at New Orleans. Subsequent hos-

pital assignments were to the Public Health Service Hospital at Stapleton, N. Y.; Georgetown University Hospital, and Children's Hospital, Washington, D. C. From 1931 to 1934 he was engaged in research work in the public health aspects of heart disease at the National Institutes of Health, research branch of the Public Health Service, and he continued his research work in heart disease at the University of Pennsylvania in Philadelphia until 1940.

The next several years Dr. Hedley spent in the study of hygienic hazards in the shipbuilding industry. During this period he also conducted surveys on industrial hygiene in Army arsenals and ordnance plants. He was Public Health Liaison Officer for the Army's First Service Command in Boston in 1943 and 1944, and in March, 1946, on a Department of State assignment, he went to France, Belgium and Germany as a medical consultant and advisor to the military.

The author of numerous medical articles, Dr. Hedley was one of the contributing authors of the "Manual of Industrial Hygiene." He was a Diplomate of the American Board of Preventive Medicine and Public Health, and held memberships in the Philadelphia Medical Society, the College of Physicians of Philadelphia, the American Medical Association, the American Heart Association, the American Public Health Association and the Association of Military Surgeons.

In addition to his widow, Mrs. Charlotte Hedley, with whom he lived at 616 South Garfield Street, Arlington, Va., he is survived by two daughters, Miss Lucile Hedley of Richmond, Va., and Mrs. Eugene S. Smithson, Jr., of Ashland, Va.; his mother, Mrs. William B. Hedley; a brother, Harold H. Hedley, and a sister, Mrs. Tyre Thomas, all of Richmond.

J. Stewart Hunter,
Assistant to the Surgeon General
U. S. Public Health Service

DR. JOHN WALKER MOORE

Dr. John Walker Moore, F.A.C.P., died in Louisville, Ky., on November 10, 1952, of hypertensive and arteriosclerotic encephalopathy. He was born in McConnellsville, S. C., on January 29, 1884, son of James Oscar and Hattie (Walker) Moore. He received the degree of B.S. from Davidson College in 1906, then attended the University of North Carolina, 1908–10, later transferring to the University of Pennsylvania School of Medicine which granted him his M.D. degree in 1912.

He took his internship at the Episcopal Hospital, Philadelphia, and upon its completion went to the University of Louisville School of Medicine in 1915 as Instructor in Pathology and Bacteriology. Thus began an association which was thereafter continuous for 37 years until his death, except for overseas service in the A.E.F. from 1917–1919. Upon his return from the Army, he became Instructor in Medicine and, in 1920, Professor of Medical Research. In 1923 he was made Professor of Medicine and Chairman of the Department, and he became Staff Executive of the Louisville General Hospital; in 1929 he also became Dean of the School of Medicine, serving in that capacity until 1949, when he resigned. Upon his resignation he was named the Alben W. Barkley Professor of Medicine, which title he still held at the time of his death.

Professionally, Dr. Moore was held in the highest esteem and earned the respect of both students and colleagues. In World War I he was Officer in Charge of Laboratories in the Hospital Center at Nantes, France, and in World War II he was Consultant to the Army Specialized Training Division. He was the kind of teacher that students never forget. He had a deep interest in research, and although his heavy teaching and administrative burdens prevented him from being as active personally in this direction as he would have liked, nevertheless he found time to participate in much worthwhile investigation. It was largely through his own ideas and inspiration that the Dye-Injection Method of measuring the cardiac output was developed in his own laboratory, and he devoted much time and thought to the experimental work

involved. His interest in research was recognized by his election to membership in the Central Society for Clinical Research (of which he was President in 1943), the American Clinical and Climatological Association, the American Society for Clinical Investigation and the Association of American Physicians. He was also a member of the Southern Medical Association (Chairman of Section on Medical Education, 1933), and the American Medical Association. He was certified by the American Board of Internal Medicine in 1937; he had been a Fellow of the American College of Physicians since 1922.

Honors came to him during his lifetime. Davidson College paid tribute to its distinguished alumnus by awarding him the honorary degree of D.Sc. in 1940. In 1936 the University of Louisville awarded him the Faculty Award of Merit, and in 1949 an honorary LL.D. In 1949 the Kentucky State Medical Association awarded him its medal for Distinguished Service. The Outpatient Clinic in the Louisville General Hospital was named "The John Walker Moore Clinic." The students named their lounge "The John Walker Moore Student Lounge." It is typical of the man that he would have been proudest of the latter, had he been able to comprehend it. Upon his retirement in 1949, his fellow faculty members, his friends, and his old Residents gave him testimonial dinners and gifts. For the occasion, Residents came from all parts of the country to do honor to their old Chief.

As an administrator, Dr. Moore was responsible for the professional operation of the Louisville General Hospital as well as Dean of the School of Medicine. Under his leadership great strides were made; not only were the physical plants of the two institutions enlarged, but to him goes most of the credit for the action of the State Legislature in 1948 in making an annual grant to the medical school. He brought many new teachers to the faculty. He not only stimulated research on the part of the teachers but he experimented with teaching methods, and in his last public address he stated that he regarded the most important need of the School to be a revision of the entire curriculum. For his contribution to medical education he was honored by being elected President of the Association of American Medical Colleges in 1945.

He met his wife, Anna Kent Moore, while in France with the A.E.F. There are three children. As a person, he had many interests and was rich in the wisdom that comes from experience. During his college days he played professional baseball to pay for his education. It was then that he earned the nickname "Farmer," which stuck to him the rest of his life. He loved a good story and told them well himself. He was intolerant of dishonesty, selfishness and pettiness. He was beloved as well as respected.

As a tribute to his memory, the University of Louisville School of Medicine has undertaken to raise an endowment fund to establish the John Walker Moore Professorship of Medicine.

J. Murray Kinsman, M.D., F.A.C.P.,
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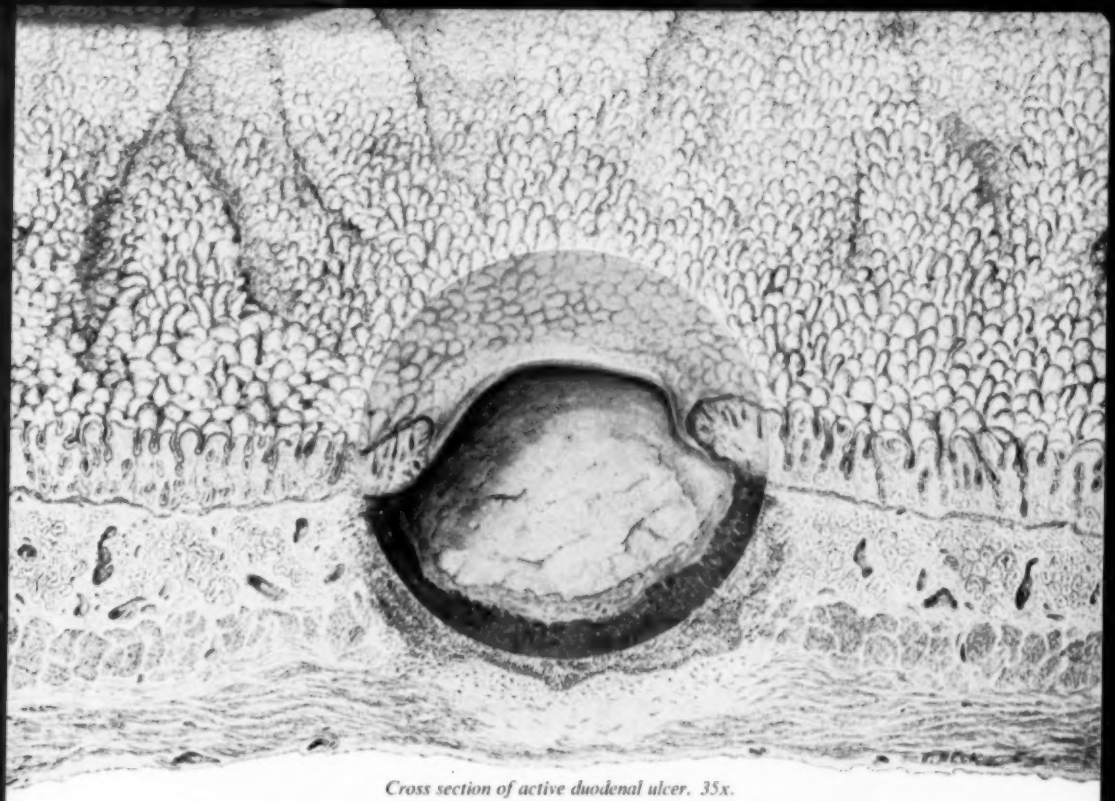

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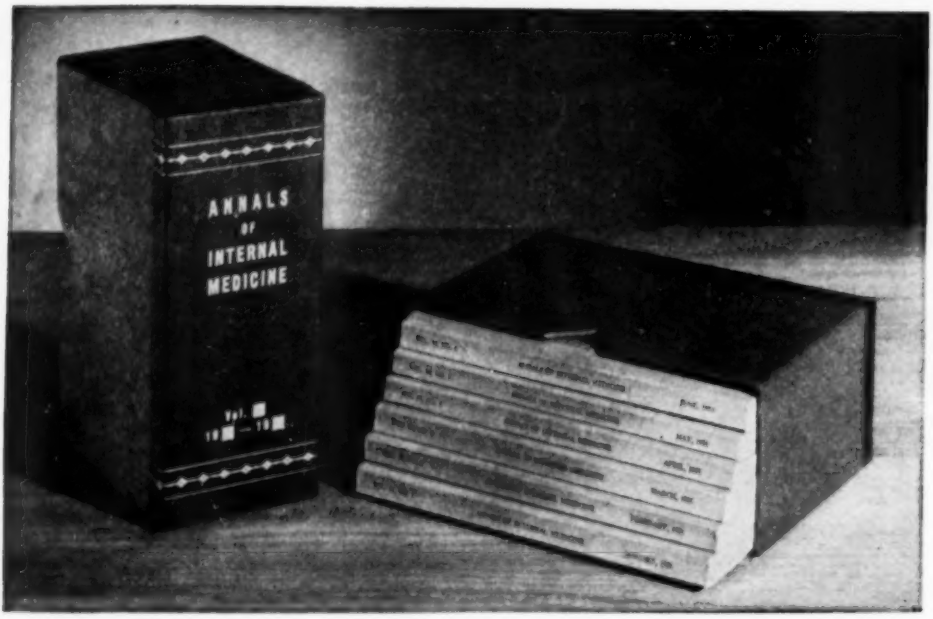

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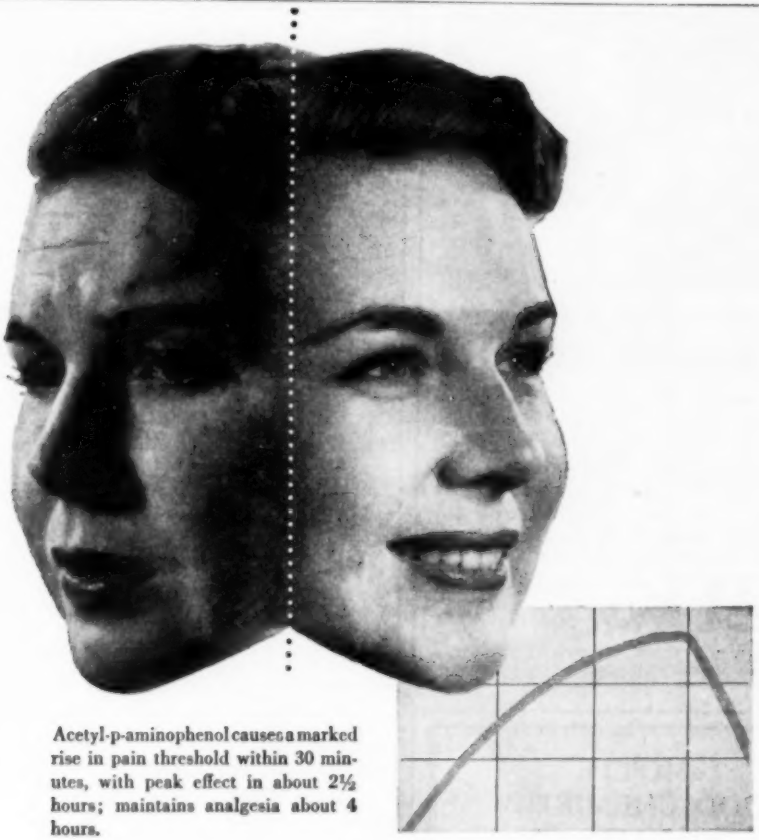

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952.
3. Perlman, A.: Angiology 3:16 (Feb.) 1952.

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4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

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